G.P.I. IN AN OBSERVATION WARD

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SYPHILIS is not in fact a " dying disease " (King 1958); but, despite warnings (Harris 1958, Mayer-Gross 1958), parenchymatous neurosyphilis is generally thought to be very rare.

During the eighteen months from April, 1957, to September, 1958, at St. Pancras observation ward, 18 cases of general paralysis of the insane (G.P.I.) were admitted. Of these 12 were hitherto untreated. In addition 1 case of juvenile G.P.I. and 2 patients with dementing illnesses and positive Kahns reactions, but negative blood Wassermann reactions (W.R.) and cerebrospinal-fluid (C.S.F.) findings, were admitted. These last 2 patients had recently had intensive antibiotic treatment for respiratory infections, and 1 died of syphilitic aortitis proven at necropsy.

Patients are admitted to the 70-bedded observation ward by the London County Council duly authorised officers and police, usually from central London and north of the Thames, on an order lasting seventeen days. Blood W.R.s and Kahn reactions are taken routinely on admission, and all patients with neurological conditions are examined by the consultant neurologist.

To show the various ways in which cases are still presenting, and to emphasise that clinical examination without serological examination is insufficient to exclude syphilis, brief case-histories of the 12 untreated and 2 recently treated cases are recorded.

Case-reports

Case 1.—A 53-year-old lorry-driver was admitted from a police-station. He was disorientated and confused, and believed he could be saved by Spilsbury. Although all reflexes were increased, his plantar responses were flexor. He had a cerebellar tremor of his left hand. There was no proprioceptic loss or pupillary signs. After treatment with chlorpromazine and penicillin he was transferred to a mental hospital, but he was so upset on hearing a membership tutorial class suggest that he may have " G.I.P.", that he returned to the observation ward. Although not psychotic, he was irresponsible. He had a valid driving licence, and would not consider alternative plans. He remained for a month on a voluntary basis, during which he was well except that he imagined himself to be one of the nursing staff. When he discharged himself he was adamant that he had no general practitioner but used the casualty department of a teaching hospital for this purpose. He had recently had his teeth extracted there for arthritis and malaise.

Case 2.—A senior clerk, aged 51, with a good war record in the R.A.M.C., had been attending his general practitioner for a year with lassitude. Three weeks before admission to hospital he attended a psychiatrist at a teaching hospital, but he failed to respond to tablets and was admitted there for two days. Because of his retardation and delusions of guilt, he was transferred to the observation ward. There were no abnormal physical signs. Mentally he was slow and dejected, believing himself to be doomed. His condition showed no improvement after a full course of penicillin, but a month later, after electroconvulsive therapy (E.C.T.), it was greatly improved. His I.Q. was then 104, and there was no evidence of dementia. He was discharged home and follow-up at the other hospital was arranged.

Case 3.—A 37-year-old Sierra Leone ex-seaman was transferred from a neurosurgical unit where he had spent a week for investigation after an epileptic fit; he had then become overactive. His hæmoglobin was 85%, white blood-cell count 7200 per c.mm., and erythrocyte-sedimentation rate (E.S.R.) 65 mm. in the first hour (Westergren). On admission to the observation ward the only abnormal physical signs were tibial scars. Mentally he was restless; he prowled around and was overactive. After being given penicillin he was found a new job and lodgings, and was discharged greatly improved.

Case 4.—A clerk, aged 47, who had graduated from one of the older universities had been having treatment for migraine at a teaching hospital. He had been remanded for a medical report by a magistrates' court. The prison medical officer regarded him as certifiably insane, and he was admitted to the observation ward from court. Physical examination showed a fine tremor only. Mentally he was euphoric, demented, and unconcerned; his I.Q. was 94. He went to a mental hospital as a voluntary patient.

Case 5.—A 72-year-old Pole had been under the care of geriatricians for seven months. He had had several little strokes in the past six years, and his son and family, who cared for him, had noted that though once he could speak six languages now he could use only his native tongue. He was grossly demented, and he had small irregular pupils and a right-sided mild hemiparesis. He went to a mental hospital on form " A " after treatment.

Case 6.—A man aged 47, a drain flusher, had just been in prison where the doctor regarded him as a psychopath with a social problem, but not as certifiably insane.

He was admitted to the general wards of University College Hospital because the pædiatrician at another hospital, where he had taken his stepson, thought he looked ill. He was febrile (103°F), with a resolving pneumonia, but he also had irregular pupils, ptosis, and an upper-motor-neurone lesion of the left arm. Mentally he was euphoric and demented. Next day, when his behaviour deteriorated and his temperature fell, he was transferred to the observation ward. From there he went to a mental hospital as a voluntary patient.

Case 7.—A single milliner, aged 42 (the only untreated female patient) of Continental extraction, had not worked for six months. She had only just been discharged from a teaching hospital after operative treatment for varicose veins.

She showed fixed irregular pupils, ankle-clonus, and a left extensor plantar response. She had grandiose delusions and was hypomanic and disorientated. She was certified.

Case 8.—A 44-year-old housewife, whose youngest child was educationally subnormal, had for six months been attending a psychiatric clinic with the label of " hypomanic reaction in a woman of low intelligence ". She had been a surgical inpatient for assessment of her incontinence.

The only abnormal physical signs were one tibial scar and a right extensor plantar response. Mentally she was overactive and elated, with occasional paranoid fears.

In view of a negative blood W.R. and adhesions in a chest radiograph, her C.S.F. was cultured but there was no growth. There was no other evidence of tuberculosis. Skull radiographs, an electroencephalograph (E.E.G.), blood-count, and E.S.R. were all compatible with G.P.I. She was certified and transferred to a mental hospital.

Case 9.—A Post Office engineer, aged 27, was admitted from a police-station in an excited condition, his personality having changed over the previous ten days. His left pupil was oval and sluggish, and he had diminished reflexes and proprioceptive sensation in the legs, but bilateral extensor plantar responses.

He was manic; he thought he was Christ and must clean up London with a hydrogen bomb. After treatment with chlor-

promazine he became quieter and agreed to go to a mental hospital as a voluntary patient.

Case 10.—A 38-year-old greyhound attendant had been forgetful for a month, and grandiose for two days. He had had an episode, eight years ago, of confusion with twisting of his left arm and mouth, which improved after six weeks' conservative treatment at home. He had served on the Continent with the Army Catering Corps during the war.

He had irregular, small, but reactive pupils, and his plantar responses were doubtfully extensor. Mentally he was glib, euphoric, and disorientated; he claimed to have sold 20,000 pigs at Smithfield. He frequently attributed his admission to the observation ward to a head injury caused by falling off his personal elephant in the Australian jungle. An E.E.G. showed diffuse abnormalities. He was transferred to a mental hospital as a voluntary patient.

Case 11.—A 44-year-old Hungarian refugee, whose mother, two siblings, first wife, and two children had been killed in concentration camps, had also been imprisoned himself for three years. Shortly after coming to England, eighteen months previously, he had learnt that his second wife had leukæmia; and this, with his inability to find employment or to learn English, produced a severe melancholia. He was treated with a course of E.C.T., vitamins, and euphoriant drugs in the psychiatric outpatient department of a postgraduate institute for eight months. He made a good recovery but was forgetful. A week before admission to the observation ward his wife died, and he became noisy, agitated, and suicidal.

Physical examination was difficult at first because he was so suspicious, but his pupils were seen to be large and unreactive to light. No other abnormal signs were found later. He was restless, agitated, and preoccupied with mourning ritual. He spoke no English, but his friends said his paranoid ideas had ceased.

After treatment with penicillin he was seen by a Hungarian-speaking psychiatrist who said the clinical picture was only one of dementia. He returned to the care of his relatives and friends.

Case 12.—An electrical engineer, aged 54, had come to England from Belgium when he was 13. He had been a good workman but four years previously had begun to steal, and he had been unemployed for the past two years. At first he lived on his savings, but he spent these rapidly. He then lived for a year on the charity of his neighbours, becoming more eccentric and grandiose, and going to the police-station to say that he had won two Nobel prizes.

He had fixed small pupils, slurred speech, tremor of his tongue, very brisk reflexes, clonus, and extensor plantar responses. He was euphoric, with delusions of grandeur.

He was certified and transferred to a mental hospital.

The table shows the findings in the C.S.F. and blood in these 12 cases before treatment. All were treated with penicillin by injection as soon as the diagnosis was made, and where possible a course of 28 million units was given. No side-effects arose. No other antisyphilitic drugs were used (Kofman 1956).

FINDINGS IN C.S.F. AND BLOOD IN 12 UNTREATED CASES OF G.P.I.

Case no.	C.S.F.				Blood	
	White cells (per c.mm.)	Protein (mg. per 100 ml.)	Lange curve	W.R.	W.R.	Kahn
1	13	150	5 5 5 5 5 5 5 5 4 4	+	+	+
2	23	70	5 5 5 3 3 1 0 0 0 0	+	+	+
3	30	50	5 5 5 4 3 2 0 0 0 0	+	+	+
4	45	100	5 5 5 3 1 0 0 0 0 0	+	+	+
5	6	130	5 5 5 5 4 2 1 0 0 0	+	+	+
6	32	90	5 5 5 5 3 1 0 0 0 0	+	+	+
7	32	110	5 5 5 5 5 5 4 4 3 2	+	+	+
8	70	70	3 4 5 4 2 1 1 1 0 0	+	−	+
9	13	50	5 5 4 3 1 0 0 0 0 0	+	+	+
10	5	40	5 5 5 4 2 1 0 0 0 0	+	+	+
11	5	65	5 5 5 4 3 2 1 0 0 0	+	+	+
12	15	70	5 5 5 5 3 2 1 0 0 0	+	+	+

The following 2 cases had been treated before admission to the observation ward.

Case 13.—A 46-year-old Cypriot had been in England for three years. After a fall from a bus, nine months previously, his condition began to deteriorate. He complained of difficulty in walking, but was sent away from a postgraduate teaching hospital as a hysteric. Three months earlier he had been in another observation ward after threatening suicide by trying to climb on the Underground track. His pupils reacted sluggishly; he was sullen, negativistic, and deluded.

After the diagnosis of G.P.I. was confirmed, he was transferred to a postgraduate teaching institute. There, despite penicillin, tranquillisers, E.C.T. and barbiturates intravenously, and although some of the staff spoke his own language, he became worse and refused food. As he was unfit to be a non-statutory patient, he was sent home and seen there by the duly authorised officer. Since the diagnosis was in no doubt, he was transferred to a mental hospital under certificate without further investigation.

Case 14.—An Irishman, aged 59, had been a commissionaire and was now a waiter. In 1946 he attended the venereal-disease department of a teaching hospital, where his W.R. was found to be positive and he was given one injection of penicillin. He failed to return for further treatment, although he knew that, as well as his gonorrhœa which was cured, he had a " touch of the pox ". He entered another teaching hospital in 1948 with lymphadenopathy, and a biopsy diagnosis of reticular sarcoma was made. According to their postal follow-up inquiry, he was well in 1958.

Towards the end of 1957, because of failing vision he went into another hospital. A diagnosis of neurosyphilis was made, and he was transferred to a postgraduate institute for treatment. The C.S.F. contained 16 white cells per c.mm. protein 125 mg. per 100 ml. Lange curve 5 5 5 5 5 3 3 3 3 3. His neurological signs were unchanged, but he began to have paranoid ideas. He was seen after discharge by the psychiatrist, and accepted an offer of treatment as a voluntary patient at a mental hospital. While this was being arranged he travelled to Dublin to implore the police to cease accusing him. Having failed to stop the hallucinations, he returned to London and was admitted to the observation ward.

He had optic atrophy, ptosis, irregular pupils, absent ankle-jerks, and diminution of proprioception, and a left extensor plantar response. He was haunted by horrible accusing hallucinations, and, apart from the accompanying depression, he showed slight dementia.

As the original voluntary-patient vacancy was for the next day, he was then transferred to the mental hospital. He discharged himself against advice, and he was readmitted to the observation ward eight days later in an unchanged state. The blood W.R. was negative and the Kahn reaction positive. The C.S.F. contained 1 white cell per c.mm., protein 50 mg. per 100 ml. Lange curve 5 5 5 5 4 3 1 0 0 0. He was returned to the mental hospital, under certificate, having started another course of penicillin.

Discussion

Neurosyphilis is probably more common than is assumed. Hughes (1959) described 10 recent untreated cases presenting to a neurosurgeon. Only cases which fail to reach general or mental hospitals, or do not get effective treatment, will be seen in an observation ward. Routine serological examination obviously still has a place on economic as well as humanitarian grounds. Psychotic episodes may arise in treated cases with a resolving or normal C.S.F., even after adequate anti-syphilitic therapy, and a more careful follow-up or a warning to the near relatives might reduce the interval before they receive psychiatric treatment.

The National Health Service seems very well suited to the needs of the peripatetic ex-patient who has no relatives to remind him to attend a follow-up clinic; for if he

changes his general practitioner his new doctor should receive his record card, including any letters from hospital. Unfortunately, however, few of these patients bother to register with a doctor, and they will probably continue to be treated as temporary patients, or at casualty departments where their past is unknown.

Summary

18 cases of general paralysis of the insane, were admitted to one observation ward within eighteen months.

The case-histories of 12 untreated and 2 recently treated patients are recorded to show the variable clinical picture.

Syphilis is by no means a dying disease, and routine serological examination is important.

I should like to thank Dr. E. W. Dunkley for his permission to publish and his criticism.

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TREATMENT OF ADVANCED CARCINOMA OF THE BREAST BY BILATERAL OOPHORECTOMY AND PREDNISONE

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FOR many years the production of hormonal imbalance has been used in the treatment of advanced breast cancer. In 1896 Beatson suggested therapeutic castration and Treves and Finkbeiner (1958) review the historical background. At this hospital, owing to the short-lived remissions following bilateral adrenalectomy and oophorectomy and the difficulty of maintaining these patients in electrolyte balance, it was decided to try the effect of bilateral oophorectomy together with corticosteroid treatment. Reports on similar methods have already been given by Nissen-Meyer (1957) and Lemon (1959); and the present report concerns the treatment of 82 patients with advanced carcinoma of the breast.

Material and Methods

All the patients selected had advanced carcinoma of the breast, and at the time of surgical castration were grouped as stage-IV cases. Most patients had been treated previously by radical surgery and radiotherapy. Several patients had hormone treatment when their metastases were first noticed, and it was not until the remissions from this treatment were exhausted that bilateral oophorectomy was undertaken. A smaller group of patients seen for the first time when their disease was already very advanced were initially treated by oophorectomy and prednisone. The ovaries were removed either at Addenbrooke's Hospital or at one of the smaller hospitals in the area served by the Addenbrooke's Radiotherapy Department. Prednisone 10 mg. b.d. was started as soon after surgery as practicable—usually within 48–72 hours.

The response to treatment was evaluated by careful clinical follow-up; subjective and objective improvement were noted, and tumour regression also measured wherever possible. The quality of remission was considered to be no less, if not more, important than the length of survival following operation.

A response was considered *satisfactory* if there was evidence of objective and subjective improvement enabling the patient to lead a relatively normal life again. Such a response was considered terminated when further palliative measures were necessary in order to prolong useful life.

A response was classed as *unsatisfactory* if improvement was purely subjective and objective improvement could not be demonstrated.

To try and find out whether any features could be used for prognosis, the quality of the response was related to: (*a*) the menopausal status of the patients; (*b*) the previous response to hormone therapy; (*c*) the presence or absence of ovarian metastases; (*d*) the length of history prior to oophorectomy.

The question of ovarian cortical stromal hyperplasia was also considered, but the changes detected in the sections could not be assessed by a sufficiently quantitative method to give any information of value. The presence of widespread liver metastases had been noted at operation in a few patients.

TABLE I—MENOPAUSAL STATUS IN RELATION TO RESPONSE

Menopausal status	No. of patients		Satisfactory response	
	" Primary "	Advanced	" Primary "	Advanced
Premenopausal ..	9	43	6	17
Menopausal	1	8	0	2
Postmenopausal ..	0	10	0	4
No information ..	6	5	3	1
Totals ..	16	66	9	24

Results

Of the 82 patients treated, 16 were in the group of " primary " oophorectomy; and, of these, 9 had a satisfactory response. 66 were treated after other forms of therapy had failed; of these, 24 had a satisfactory response with definite objective improvement, and were able to lead an active and useful life following operation; the remaining 42 patients, although many survived for many months, were considered to have had unsatisfactory responses and continued to need frequent hospital care and further palliative treatment.

Of the 16 patients treated in the first instance by castration 9 were considered to have a satisfactory response and 7 an unsatisfactory response. This group was a little more difficult to assess as they had not been under observation for any length of time before operation.

Menopausal Status

The relation of the meopausal status to the type of response is apparently not important in either group of patients treated (table I). The menopausal status was, however, assessed at the time of primary treatment of the original lesion; and thereafter some considerable time elapsed before oophorectomy, and the situation was often further modified by the use of hormones.

Previous Hormone Therapy

Hormone therapy had been prescribed before oophorectomy in 42 cases; but the response to this therapy was not always easy to assess, especially as the patients had been under the care of different doctors. The response to hormone therapy was classified as positive (i.e., the lesion classified as hormone-dependent), negative, or doubtful. In the last category the changes in the patient's condition following hormone therapy were too indefinite to allow their lesions to be classified as " hormone-

TABLE II—HORMONE DEPENDENCE IN RELATION TO RESPONSE

Hormone dependence	Unsatisfactory response	Satisfactory response
Positive	10	10
Negative	5	1
Doubtful	11	5
Not tried	16	8
Totals	42	24

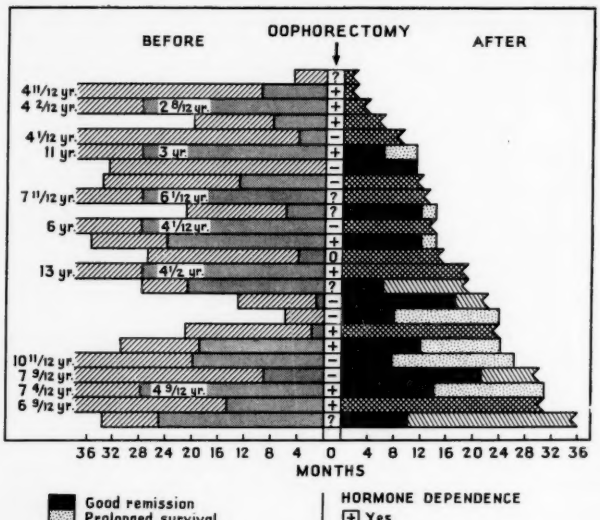

Fig. 1—Satisfactory responses of patients with advanced carcinoma of breast to bilateral oophorectomy and prednisone.

dependent ". In order to avoid bias, the response to hormone therapy was always assessed before the response to oophorectomy was known. In the satisfactory group 10 out of 16 patients were considered to have hormone-dependent lesions and in the unsatisfactory group 10 out of 26 (table II).

Ovarian Metastases

Metastases in the ovaries were found in 10 of the 44 specimens examined. The degree of destruction of ovarian tissue varied enormously, and the response to operation seemed to be unrelated to these findings (table III).

Length of History Before Oophorectomy

In both the satisfactory and the unsatisfactory groups patients were known to have had the disease for many years. The response to castration was apparently unrelated to the previous duration of the disease (figs. 1 and 2).

TABLE III—OVARIAN METASTASES IN RELATION TO RESPONSE

Histological findings	No. of specimens	Satisfactory response
Metastases present ..	10	4
No metastases	34	18
Not examined	38	11
Totals	82	33

Liver Metastases

Extensive metastases in the liver were noted at operation in 7 patients, and 2 of these subsequently had very satisfactory remissions.

Other Metastases

The time from the first treatment to the first exacerbation of the disease was known in 60 patents. Bone metastases were the first to develop in 28 patients, and 8 of these were subsequently classified as having had a good response to oophorectomy. Of the 32 patients who first presented with soft-tissue spread 13 responded satisfactorily.

Survival-time

The average survival-time for the advanced patients in the satisfactory group was 16·5 months, as against 6 months for the other advanced cases (fig. 3). In the " primary " group the patients with a satisfactory response had an average survival of 16 months, and the others 3 months. The results are summarised and the quality of remission together with the survival-time for each patient are shown in figs. 1, 2, and 4.

Case-records

The following 3 case-records illustrate the quality and the length of survival in a really satisfactory remission.

Case A.—A childless married woman of 42 who noticed a lump in her breast in June, 1949. 6 months later she reached hospital and had a radical mastectomy for a stage-II carcinoma of the left breast. The histologist reported a mucoid papillary carcinoma of the breast. A radical course of postoperative X-ray therapy was planned for the patient, but this treatment was never completed as she developed infective jaundice. She remained in good health for five years, after which lung metastases developed in July, 1955. She was treated with testosterone propionate intramuscularly and obtained a good clinical remission for a year, although there was no improvement in the appearance of the metastases in chest X-ray films. At the end of the year her condition worsened and radiography showed extension of the chest metastases.

She had a bilateral oophorectomy in September, 1956, after which she had a temporary improvement of six weeks' duration. Owing to a misunderstanding prednisone was not administered until 8 weeks after oophorectomy, when she was

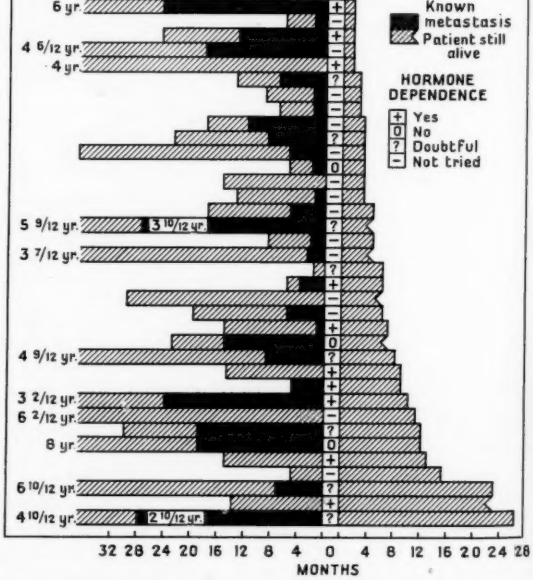

Fig. 2—Unsatisfactory responses of patients with advanced carcinoma of breast to bilateral oophorectomy and prednisone.

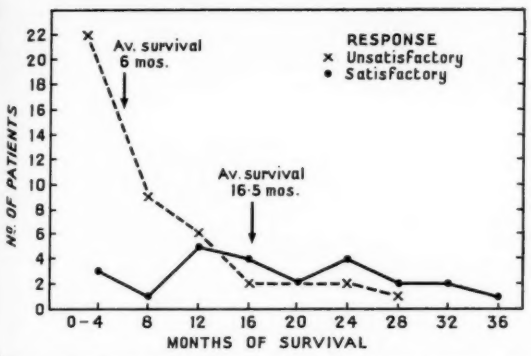

Fig. 3—Distribution of satisfactory and unsatisfactory responses in relation to survival-time.

again distressed and was very dyspnœic at rest. Prednisone 20 mg. b.d. was then administered. Metastases in her chest steadily improved, and after 6 months the prednisone was reduced to 10 mg. b.d.

In the 33 months since oophorectomy her condition has continued to improve, and the last chest film shows no evidence of metastases. She is a little "moon-faced" but is able to lead a normal life. X-rays of the chest are shown before and after treatment in fig. 5.

Case B.—A married woman of 47 with 1 child had had a lump removed from her right breast 12 years previously by local excision. In May, 1955, she was referred with "sciatica", and radiography showed multiple metastases throughout her pelvis and spine with collapse of D11 vertebra. She also had a clinically malignant local recurrence of a breast tumour.

She was treated with palliative doses of X rays to her bones and injections of testosterone propionate, and had a fair remission with almost complete relief of pain. This remission lasted about 2 years, after which pains returned. She was admitted in October, 1957, with almost complete paraplegia due to further vertebral collapse.

Bilateral oophorectomy was performed and in October, 1957, prednisone 10 mg. b.d. was started 6 days post-operatively.

Since then her condition has steadily improved, and the only residual sign of paraplegia is a slight weakness in the left leg, which does not prevent her from leading a normal life and running her home. Her weight has increased a stone since her operation, but this does not worry her. Radiography shows little change since the oophorectomy, but there is some sclerosis of the metastases.

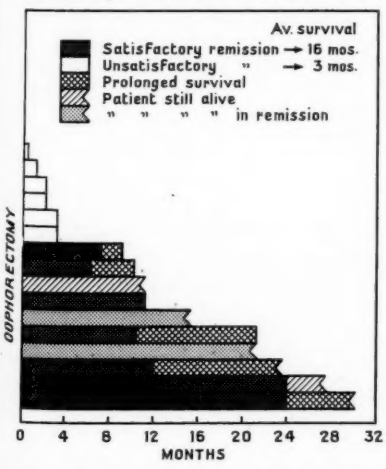

Fig. 4—Response of patients with advanced carcinoma of breast to primary treatment with bilateral oophorectomy and prednisone.

Case C.—A married woman with 3 children first attended hospital in October, 1954. For 2 years she had noticed a lump in the left breast, and a lump had been found in the right breast 6 months previously. There was a 4-month history of backache. Clinically there was a large ulcerated scirrhous carcinoma of the left breast with fixed axillary and supraclavicular glands. On the right the carcinoma and the axillary nodes were mobile. There were widespread skin metastases over the trunk, and bone-marrow aspiration showed numerous malignant cells. As the patient refused bilateral adrenalectomy, intramuscular testosterone propionate was given, and the patient had a good remission until July, 1956. At this time the skin nodules were increasing in size and abdominal ascites was developing. There was slight improvement after the testosterone injections were stopped, but by May, 1957, ascites was severe, and bilateral oophorectomy was performed on May 24. Prednisone 10 mg. b.d. was started 5 days after operation, and the patient improved and remained well until September, 1958, when ascites once more became a problem. Intraperitoneal gold in October, 1958, gave another short remission until February, 1959, when the patient started to deteriorate rapidly; she died in April, 1959, some $4^1/_2$ years after attending hospital with a very advanced neoplasm with bone-marrow involvement.

Discussion

Previous critical assessments of hormone treatment of advanced carcinoma of the breast have nearly all reported 30–40% of good results (see Treves and

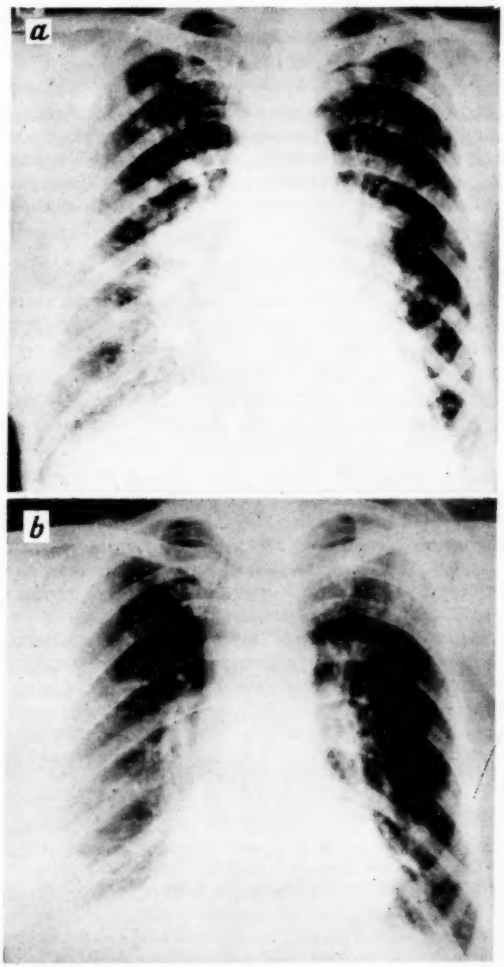

Fig. 5—Case C: (*a*) 1 month before oophorectomy; (*b*) 30 months after oophorectomy.

Finkbeiner 1958). It seems that 30–40% of patients are likely to have "hormone-dependent" tumours; but the type of hormone treatment which gives the most satisfactory results is not yet clear, and as yet there is no method of determining which patients are likely to have "hormone-dependent" tumours.

The present series indicates that patients who have had a remission following androgen treatment are likely to get a further remission from oophorectomy and prednisone. However, failure to respond to androgen does not necessarily indicate that oophorectomy will fail, and as yet we have no method of selecting patients who are likely to respond satisfactorily to oophorectomy.

The advantages of bilateral oophorectomy followed by administration of prednisone are, firstly, the comparatively minor nature of the operation with an average stay in hospital of 10 days, and, secondly, the prednisone besides helping to suppress the tumour imparts a feeling of well-being. In addition, administration of low doses of prednisone does not require much supervision. Operation is necessary because X-ray castration does not completely stop ovarian function. A patient in pain preoperatively who responds to operation will probably be completely relieved of pain as soon as she has recovered from the anæsthetic. The only disadvantage of this treatment seems to be the increase in weight due to fluid retention, but this is an embarrassment to only a minority of the patients.

We do not know how the prednisone acts. Through the pituitary it may suppress adrenal function, or it may act directly on the tumour. Experience has indicated that 20 mg. daily is about the optimum dose, and we think it likely that its action is not simply that of a euphoriant.

Summary

82 patients with advanced carcinoma of the breast were treated by bilateral oophorectomy and administration of prednisone.

16 patients were treated by "primary" oophorectomy, and 9 of these had a satisfactory response: their average survival-time was 16 months, compared with 3 months for the 7 patients in the unsatisfactory group.

66 patients were treated when remissions by X-ray and/or hormone therapy were exhausted. 24 of these had a satisfactory response with an average survival-time of 16·5 months, compared to 6 months for the 42 other patients. Of 16 patients showing a satisfactory response, 10 were found to have hormone-dependent tumours, whereas of 26 showing an unsatisfactory response only 10 were considered to have hormone-dependent tumours.

The menopausal status, the presence of ovarian metastases, and the length of history before oophorectomy or liver involvement appeared to be of no definite prognostic significance.

Bilateral oophorectomy and administration of prednisone are useful in the treatment of patients with very advanced carcinoma of the breast.

We would like to thank our many colleagues in this area who have directly and indirectly helped with this project, and Prof. J. S. Mitchell for his helpful discussion of this paper.

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TREATMENT OF INGUINAL HERNIÆ

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St. Thomas's Hospital has long been associated with the medical care of members of the Metropolitan Police Force. As a result it has been possible to achieve a high follow-up rate after these patients leave hospital.

The results of operations for inguinal hernia on members of the Metropolitan Police were reviewed by N. R. Barrett in 1934, and by A. G. McPherson in 1943, on behalf of Sir Max Page (1934, 1943).

In view of the new techniques introduced in recent years it was thought that a further review might be of value. An attempt was made to examine all Metropolitan policemen, totalling 266, who had been operated upon for inguinal hernia between 1945 and 1954, the follow-up period being between 12 and 4 years.

The great majority presented themselves for examination. 23 who had retired from the Force and lived far away were seen by their own doctor; a few were unresponsive and had to be visited in their own homes. All those included in this series were medically examined. Postal questionnaires were not used.

Findings

Of the 266 patients, 5 had died of intercurrent disease and 5 were untraced (2 in the U.K., 1 in Canada, 1 in the U.S.A,. and 1 in Australia).

The 256 who were successfully followed up had an average age at operation of 40 years (range 21–60).

Inguinal herniæ operated on numbered 335 (i.e., 79 had bilateral herniæ). Recurrences totalled 48 (14·3%). The recurrence-rate according to type of hernia is shown in table I. Tables II–IV show the recurrence-rates for indirect, direct, and recurrent herniæ related to the types of operations.

No definite reason was found for the choice of repair operation. It appeared to depend on the type of operation in favour at the time, and on the particular surgeon's beliefs, except that herniotomy and plication was reserved for very minor weakness of the posterior wall, and that the Bassini operation was not done on the bigger direct herniæ.

TABLE I—RECURRENCES IN 335 HERNIÆ

Type	No.	Recurrences
Indirect	204	29 (*14·2%*)
Direct	94	17 (*18·3%*)
Recurrent *	37	3 (*8·1%*)

* First operation at St. Thomas's Hospital in 28, elsewhere in 9, cases.

TABLE II—RECURRENCES IN 204 INDIRECT HERNIÆ

Operation	No.	Recurrences
Herniotomy	54	9 (*16·7%*)
Herniotomy + plication of transversalis fascia	13	2
Bassini	26	8 (*30·8%*)
Bassini + Tanner slide	10	2
Gallie	44	3 (*6·8%*)
Floss-silk darn *	12	2
Bloodgood	3	0
Nylon darn	40	2 (*5%*)
Others	2	1
Total	204	29 (*14·2%*)

* Method used by one surgeon only.

TABLE III—RECURRENCES IN 94 DIRECT HERNIÆ

Operation	No.	Recurrences
Herniotomy + plication	3	0
Bassini	12	3
Bassini + slide	5	1
Gallie	28	6 (*21·4%*)
Floss-silk	6	2
Bloodgood	5	0
Nylon darn	32	4 (*12·5%*)
Others	3	1
Total	94	17 (*18·3%*)

TABLE IV—RECURRENCES IN 37 RECURRENT HERNIÆ

Operation	No.	Recurrences
Herniotomy	2	0
Bassini	4	1
Bassini + slide	1	0
Gallie	5	1
Bloodgood	1	0
Nylon darn	18	0
Others	6	1
Total	37	3 (*8·1%*)

These results compare with:

Barrett, 1934.—206 cases treated predominantly by Bassini or Foster technique, with a recurrence-rate of 20% for indirect herniæ and 25% for direct herniæ.

McPherson, 1943.—174 cases, treated mainly by herniotomy or Gallie's operation, with a total recurrence-rate of 14·9%—indirect 12%, direct (17 cases) 35·3%.

Discussion

The criterion of a recurrent hernia was considered to be the presence of an expansile cough impulse. It has not seemed reasonable to defer diagnosing recurrent hernia until this caused disability: indeed, in this series over 10% of recurrences were unnoticed by the patient. Asymptomatic recurrences make reviews which are not based on physical examination liable to error.

The persistence of a high recurrence rate is disturbing, and we feel that this series reveals features which could point the way to better results:

Type of Operation

Case-histories were inadequate to correlate the type of operation with the state of the posterior wall of the inguinal canal. Where, however, a repair has been considered necessary, the best results appear to follow the nylon-darn, now commonly used in place of the Gallie, and the Bloodgood types of techniques. Unfortunately there were too few of the latter to allow a firm conclusion to be made. The Bassini operation has been associated with a high incidence of recurrence at this hospital, but the figures are too small to determine whether the results varied with the suture materials used.

Priority

Inguinal herniæ are often relegated to the end of the list and are too often done by inexperienced operators without adequate supervision. The recurrence-rate for indirect herniæ operated on by housemen was 20%, compared with 9% by registrars.

The high incidence of recurrence following herniotomy alone can be partly ascribed to bad choice of operation, as many as a third being done on patients between the ages of 40 and 59. In this series simple herniotomy has a low recurrence-rate up to the age of 39, after which it rises steeply.

It is also difficult to escape the conclusion that the remarkable results obtained on recurrent herniæ are partly related to the extra care which is called forth by these herniæ.

Further information acquired from this series confirms that postoperative sepsis is associated with an increased recurrence-rate, and that neither simultaneous repair of bilateral herniæ nor ambulation during the first postoperative week influences recurrence-rate. Almost all recurrences were diagnosed within four years of operation; the majority showed themselves by the end of the first year.

The results did not show an increasing liability to recurrence with increasing age of the patient, but "invisible" factors were at work here: for example, the younger patients with the simpler herniæ were mainly operated on by younger surgeons.

There was 1 sinus following the nylon darn repair.

It was not possible to determine whether prophylactic postoperative administration of antibiotics or sulphonamides influenced the sepsis-rate.

Conclusion

The results of this review are disappointing. Being the unselected results of a number of different surgeons, they probably represent the state of affairs in most hospitals where the treatment of herniæ is given similar priority.

Greater attention to the care of these patients is likely to improve results. The final decision as to which operation should be performed should be made when the tissues are exposed at operation, and only by someone with experience.

The nylon darn and Bloodgood types of operation have given good results. Simple herniotomy for patients with a sound posterior wall gave low recurrence-rates up to the age of 39. The Bassini operation, although apparently successful in certain hands, does not appear to give good results at this hospital.

Our thanks are due to the surgeons at St. Thomas's Hospital for permission to carry out this investigation, and to the staff of the Medical Branch, Scotland Yard, for help in tracing the patients.

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LEISHMANIASIS ACQUIRED BY CONTAGION

A CASE OF MARITAL INFECTION IN BRITAIN

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THE transmission of all forms of leishmaniasis depends ordinarily upon phlebotomus sandflies. We owe our freedom from the infection in this country to our climate, which does not suit the insect vectors, and to the absence of any reservoir of infection in the population or in animals. The occasional cases which we see originate elsewhere—most of them are examples of the so-called oriental sore, and the diagnosis is readily made when the patient is known to have come from a part of the world where this disease occurs. A knowledge of geographical pathology and of the symptomatology of exotic diseases is becoming more and more important as travel becomes easier, faster, and more necessary, and the diagnostic importance of taking an accurate history of patients' oversea journeyings is obvious.

The American Geographical Society's (1954) map of the world distribution of leishmanial infections shows that *cutaneous leishmaniasis* (oriental sore) occurs in parts of Europe, Africa, and Asia. It is found in the coastal belt of the countries of the whole Mediterranean basin, across Turkey to the Caspian Sea, down through Iraq to the Persian Gulf, across Iran, Afghani-

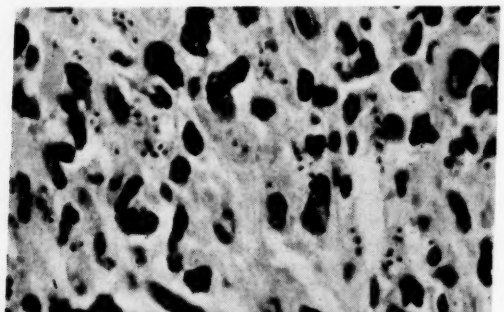

Fig. 1—Biopsy of vulvar lesion: the leishmanias in the macrophages of the inflammatory exudate are easily seen. (Hæmatoxylin-eosin; ×600.)

stan, and Turkistan, across Pakistan and northern India, and in Ceylon. It occurs in West Africa from the Gambia to the Cameroons, and in East Africa—particularly in Ethiopia. Occasional cases have been recognised in other parts of West and East Africa, in Malaya, and in various parts of eastern Asia. Isolated cases have also been reported nearer Britain, in Portugal and northern Spain.

It is not proposed to refer particularly to *visceral leishmaniasis* (kala-azar) or to *American leishmaniasis* in this paper. It may be noted, however, that the geographical distribution of visceral leishmaniasis is a good deal wider than is usually realised, and yet overlaps remarkably little with that of oriental sore. An account of leishmaniasis in all its forms is readily accessible in *Manson's Tropical Diseases* (Manson-Bahr 1954), and only some aspects relevant to the cases reported in this paper will be mentioned here.

Cases of cutaneous leishmaniasis have been reported in Britain from time to time, and particularly since the late war (Conrad et al. 1950, Howell 1957, and others, including cases shown at society meetings, and particularly at the Section of Dermatology of the Royal Society of Medicine). The patients have usually been visitors or immigrants from areas where the disease is endemic. From the geographical summary given above it may be seen that some of these areas are commonly enough visited by British businessfolk or holidaymakers; the diagnosis of cutaneous leishmaniasis is worth considering when any patient with an indolent skin lesion has been in such parts. The length of stay in an endemic area before infection takes place need be no longer than the few moments taken by a sandfly to feed.

The protozoon which causes leishmaniasis was first recognised in a soldier who had come home to this country from India.

Leishman (1903) found the organism, in 1900, in smears from the spleen of this man, who had died of kala-azar in the Royal Victoria Hospital in Netley, Hampshire. The patient had contracted the disease during service in Dum Dum, the station in Bengal which gave the disease one of its names. Publication of Leishman's (1903) observation led Donovan (1903) to record his own independent discovery of the organism, which he had found in Madras in 1903 in smears from the spleens of three patients at necropsy and of one living patient. It is appropriate that the names of these two men are coupled in the common designation of the parasites as Leishman-Donovan bodies and in the name of the most important species, *Leishmania donovani*. Wright's (1903) discovery of the causative organism of oriental sore, now known as *L. tropica*, followed shortly afterwards. The other main varieties of *Leishmania* are *L. infantum*, which causes visceral leishmaniasis of children on the Mediterranean littoral, and *L. brasiliensis*, the cause of American leishmaniasis. In addition, mention must be made of *L. canis*, which causes leishmaniasis in dogs, particularly in Mediterranean lands but also elsewhere—the infection has, for instance, been found in dogs in the region of Paris (Guilhon 1950) and in Brittany (Guilhon and Loge 1950). It has been suggested that canine leishmaniasis may be a reservoir for human infection. There is some doubt whether all these named species of *Leishmania* really qualify to be considered as specifically distinct from one another.

The main purpose of this paper is to report a case of leishmaniasis which is unprecedented in that the patient had never been out of the British Isles before she acquired her infection. Her case was also remarkable in that the lesion, which was on the vulva, was almost certainly the result of direct contagion: her husband had a symptomless recurrence of visceral leishmaniasis contracted several years earlier in north-eastern Africa. As the clinical and laboratory management of her case was bedevilled by a series of avoidable mistakes, before the correct diagnosis was made, it may be politic to make known that the investigations and treatment were carried out in hospitals and laboratories which are not in London, and that she developed the lesion in 1955. Both patients know the full circumstances of the mistakes made, and they and the doctors concerned have encouraged publication of this account.

Case-records

A woman, aged 38, noticed a small, rather itchy papule a little behind the vaginal orifice and to one side of the midline. As it was enlarging she went to her doctor—her husband's brother—a month later. The lesion was then a shiny, purple, dome-shaped nodule, a centimetre in diameter, painless, and with a small, central excoriation which the patient attributed to chafing by sanitary towels. Nothing was done about the lesion at that time. A month later it was almost twice as large: the central erosion had become a round, sharply outlined, steep-sided but quite shallow ulcer, about a centimetre across, with a grey base. There was now a group of moderately enlarged, firm, painless, lymph-nodes medially in the groin on the same side. Her doctor diagnosed primary syphilis although he had never seen a chancre at that time.

Blood for a Wassermann reaction was sent to a laboratory where, it so happened, it was still the practice for the entire Wassermann procedure to be carried out by the pathologists. Unfortunately, the senior registrar whose turn it was to do the Wassermann tests had no previous experience of complement-fixation techniques, and as he had just been newly appointed to his job he did not like to admit to this gap in his training. It has become clear that in this patient's case he must have either misconducted the test or misinterpreted its result, which was reported to her doctor as positive.

The patient was then seen by a gynæcologist, who agreed that the lesion could be syphilitic and recommended appropriate treatment. He did in fact say that the Wassermann reaction should be repeated and a Kahn test done as a confirmatory precaution before treatment was started, but this advice was overlooked and a month's course of penicillin was begun without further ado. The patient had never had treatment with penicillin before. During the last few days of the course she felt unwell: she became somewhat feverish and developed joint pains and an erythematous rash on her face and body. The significance of this syndrome was not realised at the time, but it was almost certainly a reaction to penicillin, to which she is now known to have become sensitive. Her Wassermann reaction becomes positive whenever a penicillin reaction is provoked (her Kahn-test result is negative at all times). This may explain why the Wassermann reaction at the end of the month's course of penicillin was reported (this time, by chance, in a different

laboratory) as " $+\pm$ "; the Kahn test, done then for the first time, was negative.

Although by then the local lymphadenopathy had disappeared the vulvar sore was larger than before the course of penicillin. For some reason which is no longer clear a darkfield examination was carried out now, for the first time; it was reported as negative.

Both the patient and her husband denied having had sexual intercourse with anyone else. As the husband had no genital lesions and his Wassermann and Kahn reactions were negative his wife's truthfulness seemed to be in doubt; he left home. Fortunately, it was at last beginning to be realised that there was something inconsistent between the clinical findings and the supposed diagnosis of syphilis. Biopsy of the ulcer was therefore carried out, five weeks after the end of the course of penicillin and eighteen weeks after the patient first noticed the lesion.

The sections showed a chronic inflammatory reaction in the dermis, nondescript for the most part but with a small area in which typical Leishman-Donovan bodies were readily recognised within macrophages (fig. 1). Their presence was confirmed in stained films of exudate from the ulcer (fig. 2), and they were also well demonstrated by darkfield examination. When the technician who had been entrusted with the first darkfield examination was shown the leishmanias in the later preparation he recognised at once that he had seen them in the earlier specimen. He explained that he had not drawn anyone's attention to them because he had only been told to look for treponemas. Attempts were made to cultivate the organism from fluid obtained by puncture of the unbroken skin over the periphery of the lesion: they failed because of bacterial contamination.

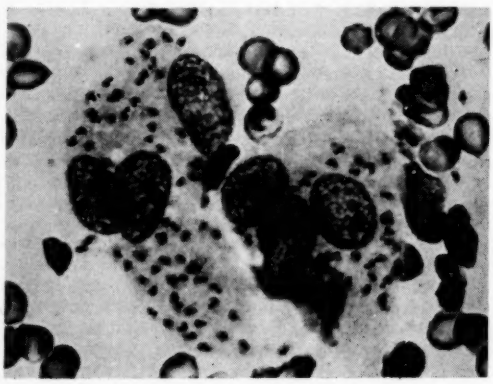

Fig. 2—A group of leishmania-laden macrophages in a film of exudate from the vulvar lesion. (Leishman's stain; ×900.)

As the patient had never been out of the British Isles it was necessary to consider various seemingly unlikely ways by which she could have become infected. There was no immediately obvious solution of this mystery, although all sorts of possible sources of infected vectors were looked for in her environment. By this time it had been possible to get in touch again with her husband, who had gone abroad: he returned home at once with the answer, which unwittingly he had all along possessed, in the form of a history of kala-azar. He had contracted kala-azar while on service in the Sudan, Ethiopia, and Uganda in 1941 or thereabouts. This had been only erratically treated, owing to the exigencies of the times and of his work, and, later, of detention as a prisoner-of-war. The drugs used were probably antimony potassium tartrate and ethylstibamine (' Neostibosan '). By 1944 he was pronounced cured, only to develop typical post-kala-azar dermal leishmaniasis a year later. This in its turn cleared up on treatment with pentamidine isethionate (' Lomidine '), and from then onwards he was free from all symptoms. He married in 1953, eight years later. His wife's leishmanial ulcer developed in 1955, two years after their marriage.

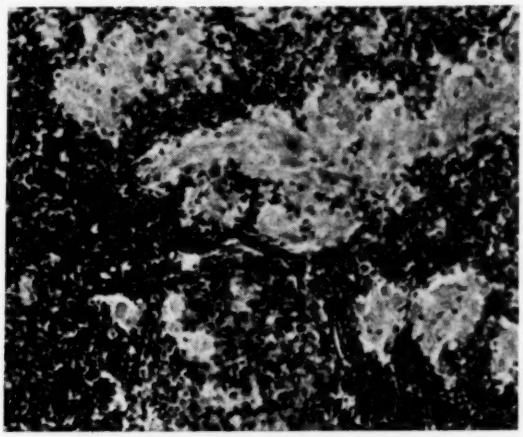

Fig. 3—Focal histiocytosis in lymph-node biopsy specimen from the husband of the patient whose infection is illustrated in figs. 1 and 2. (Hæmatoxylin-eosin; ×150.)

Although at this time he was completely symptomless and for ten years had been aware of nothing amiss with his health, examination showed that the tip of his spleen was palpable four centimetres below the costal margin; his liver was palpable a centimetre below the costal margin, and there was generalised lymph-node enlargement. It seems likely that a complete physical examination instead of the perfunctory inspection of his genitalia at the time when his doctor looked for evidence of syphilis could have led to a prompt appreciation of the true condition of his health and of the nature of his wife's ulcer. When examined he was afebrile. The serum-protein levels were normal. Napier's formol-gel test and the urea-stibamine test were negative. Apart from slight granulocytopenia his blood was normal. The marrow was not examined. Biopsy of an axillary lymph-node showed many discrete, small foci of histiocytosis (fig. 3): it was evident that the histiocytes contained minute particles, and at higher magnifications these were clearly recognisable as leishmanias (figs. 4a and b). They were well seen in films of fluid from the node, and they were successfully cultivated in " N.N.N." (Novy, MacNeal, and Nicolle medium), in which typical flagellate forms (" leptomonads ") developed abundantly within five days on incubation at 22°C. He was treated with pentamidine isethionate (0·2 g. intravenously daily for ten days). A month later there was no detectable clinical abnormality, and this is his present state. Before the course of treatment attempts were made repeatedly but unsuccessfully to demonstrate leishmanias in his urine, prostatic secretion, and semen.

The woman's lesion healed satisfactorily when she was given a course of urea stibamine (0·2 g. intravenously daily for ten days); it has not recurred (January, 1960). She and her husband have re-established their home and have had their first child, which was born uneventfully eighteen months after cure of the ulcer.

Discussion

Clinicopathological Management

There is no need to discuss the reasons for the mistakes in the investigation and management of the woman's case. Although it is understandable how medical training nowadays might be completed without the student having an opportunity to see a primary syphilitic chancre, it is disquieting that any doctor could consider a single positive report of a single serological test as adequate grounds for telling a patient and her husband that she had syphilis, with all the potential implications and consequences. It is unfortunate that the gynæcologist should have prescribed treatment for primary syphilis without asking

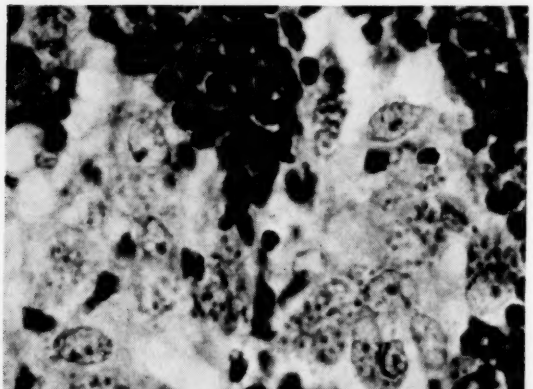

Fig. 4a—Higher magnification of a field like that in fig. 3 (same preparation): the leishmanias can be seen in the pale cytoplasm of the histiocytes. (Hæmatoxylin-eosin; ×650.)

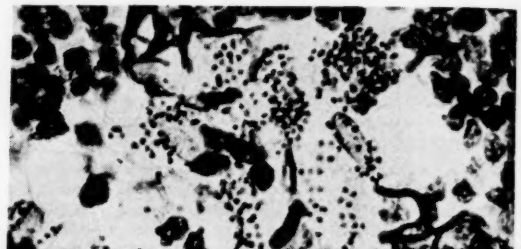

Fig. 4b—A field comparable to fig. 4a, but from a silvered preparation in which the parasites are more obvious although the details of their structure are obscured. (Robb-Smith [1937] method for reticulin; ×650.)

for darkfield investigations in addition to the confirmatory blood tests. In any case, to neglect nowadays such a clear indication for the *Treponema pallidum* immobilisation test is a major oversight.

It was interesting that the conduct of the pathological investigations should have disclosed two extremes in modern laboratory practice. In one laboratory the actual interpretation of darkfield examinations was delegated to a technician; in the other laboratory the pathologists personally undertook every step in the performance of the Wassermann reaction and not merely the interpretation of the results. Paradoxically, in the laboratory in which there was this insistence on the pathologists' personal responsibility for carrying out the Wassermann procedure it was not regularly the practice to put up parallel confirmatory tests unless the Kahn test was specifically asked for, which was not done in this case.

Latent Recurrent Kala-azar

I have not been able to find any previous instance of a recurrence of visceral leishmaniasis so long after what had been considered successful treatment. The patient's freedom from symptoms was another exceptional feature of his recurrent infection.

The histological pattern shown by the lymph-node biopsy was precisely that seen in cases of acquired toxoplasmic lymphadenitis in adults (Bang 1957, Piringer-Kuchinka et al. 1958). Only the presence of the leishmanias distinguished the picture from that of toxoplasmosis; the morphological characteristics of the organisms under the oil-immersion objective were unmistakable. In some cases it can be difficult to distinguish confidently in hæmatoxylin-eosin preparations between leishmanias and other particulate bodies, particularly *Histoplasma capsulatum* (Woo and Reimann 1957). Recently, in a personal observation, groups of the small-spore form of *Blastomyces brasiliensis*, separated from their parent yeasts and engulfed by macrophages, were mistaken for *Leishmania brasiliensis* in a biopsy specimen; the lesion was a mucocutaneous granuloma which developed some months after the patient had returned home to this country following a year's stay in Brazil. The well-known Flemming bodies (particulate nuclear debris) in lymphoid follicles, which are notoriously liable to be mistaken for histoplasmas, may also be misinterpreted as leishmanias. Romanowsky stains are not as helpful in identifying leishmanias in histological preparations as they are in films: the periodic-acid/Schiff reaction is often more useful, readily distinguishing fungi like histoplasma from leishmanias (leishmanias may contain particles which give this reaction; but these are minute, and confusion should not result). In all cases in which it is possible—and that should be the vast majority—film preparations should be made whenever the diagnosis of leishmaniasis is considered, for they will readily enable any leishmanias which are present to be correctly recognised.

Excision of lymph-nodes for the diagnosis of leishmaniasis was advocated many years ago by Cochran (1912), who, however, recommended this procedure merely so that films could be made from them. Cole (1943–44) reviewed 60 cases of kala-azar in the Kapoeta area of East Africa; this is the area where Ethiopia, Kenya, and Uganda meet, and it was probably here that the man whose case is recorded above became infected. Cole mentioned that half of his patients showed lymph-node enlargement, usually in the inguinal and femoral groups. In one case, indeed, lymphadenopathy was the presenting manifestation; leishmanias were found by lymph-node puncture in 12 out of 27 cases in which this investigation was carried out. Kirk and Sati (1939–40) demonstrated the organisms in films of juice obtained by needling apparently normal lymph-nodes in Sudanese cases of kala-azar. Cole (1943–44) found urea stibamine to be the most effective drug in his cases. Post-kala-azar dermal leishmaniasis developed in 17 of the 38 patients in his series who survived: the parasites were demonstrated in scrapings from the skin lesions in 8 out of 12 cases investigated. During the period in which he studied the 60 cases of visceral infection he saw only 1 case of oriental sore.

In contrast with cases in the Sudan, where Kirk and Sati (1939–40, 1940–41) found that there is often no latent period between visceral involvement and involvement of the skin and lymph-nodes, Napier (1935) found in India that the organisms can scarcely ever be demonstrated in the skin and lymph-nodes during the visceral stage of kala-azar. Post-kala-azar dermal leishmaniasis, which was first described by Brahmachari (1922), usually appears a year or two after the visceral disease has subsided, and particularly in cases in which the latter has been inadequately treated: it is easily distinguishable clinically from oriental sore, differing from this condition specially in its more widespread involvement of the skin and in the multiplicity of the lesions, which are commonly nodular. In view of the lymph-node involvement in the case reported in this paper, and of the patient's earlier history of post-kala-azar dermal leishmaniasis, it is interesting to learn that both leishmanial lymphadenitis and post-kala-azar dermal leishmaniasis are seen more frequently in north-east Africa than in other parts of the world.

It is remarkable that the woman's lesion took the form of an oriental sore, typical of infection by *L. tropica*, whereas her husband's disease was of the visceral type associated with infection by *L. donovani*. Shapiro and Btesh (1939–40) mentioned the case of an Arab child in Palestine who simultaneously had kala-azar and cutaneous leishmaniasis of the oriental-sore type: they raised the question whether this boy was doubly infected with *L. donovani* and *L. tropica* or whether *L. donovani* was the cause of both the visceral and the cutaneous disease. It would have been instructive in this woman's case to know whether the transitory inguinal lymph-node enlargement was due to leishmanial infection, as was her husband's lymphadenopathy, or whether it was unspecific.

Transmission of leishmaniasis

There seems to be no doubt that the infection in this case was passed by sexual intercourse. There are very few acceptable reported instances of person-to-person leishmanial infection and none of transmission by contagion.

One foreign author cites Leishman as his authority for stating that the disease can be spread venereally. I have been unable to trace such a statement in any of Leishman's writings, and it seems possible that a comment which he made when writing about the ætiology of kala-azar has been misread: "In the presence of these important gaps in our knowledge of the life-cycle of the parasite any description of the ætiology of the disease must be, in the main, speculative. There appears to be little doubt that the disease is spread by human intercourse, though not by direct 'contagion' in its strict sense" (Leishman 1912). It is clear that sexual intercourse was not implied.

Shortt (1945–46) reviewed the ways in which leishmaniasis might be spread, and he noted that person-to-person transmission was theoretically possible. The organisms may be present in a viable state in nasal secretion and in urine, and they can survive for a day or more in moist soil and for several days in milk. They also appear to be able to withstand desiccation for a few hours. Shortt pointed out that infection can be shown by experiment to follow introduction of the parasite into the mouth or conjunctival sac, thus indicating the possibility of transmission by ingestion or by droplet infection.

Firth (1912) and Berberian (1939–40) reviewed the deliberate, and often traditional, practice of inoculating children and others with oriental sore in order to provide some measure of immunity and to try to ensure that the often unsightly scar of the healed lesion should be in an inconspicuous site. There is no doubt that under these conditions person-to-person infection can occur. Under natural conditions, however, leishmania requires to spend a part of its life-cycle within the body of the phlebotomus vector, undergoing metamorphosis and multiplying before the fly can transmit the infection to a fresh victim. It may be noted that Leishman's (1912) remarks on the ætiology of the disease, quoted above, were written before Mackie's (1915) suggestions about the role of the sandfly as vector, and long before it was finally proved that the infected flies could in fact transmit the disease. Adler (1939–40) successfully transmitted kala-azar to one of five patients with advanced malignant disease whom he inoculated with cultures of *L. donovani*: the incubation period was uncertain but did not exceed five months. Later, Swaminath et al. (1942) transmitted Indian kala-azar to man by the bite of infected sandflies in each of five experiments: the incubation period was between nineteen and thirty weeks or thereabouts. Other experimental studies have confirmed that leishmaniasis can be conveyed in this way, provided that enough time is allowed for the protozoon to complete its cycle of development in the infected phlebotomus before attempting to transmit the infection, and provided that the inoculated volunteers or animals are kept under observation long enough to allow the presence of infection to be recognised. There is no longer any doubt that natural infections with leishmania, including familial and household infections, are ordinarily attributable to the bite of infected sandflies.

Senekji and Beattie (1940–41) studied the development of experimentally produced oriental sores in man. From observations on over 200 cases they found that the incubation period after an intradermal injection of three million leptomonad forms from cultures of *L. tropica* ranged from under two weeks to eight weeks. A single inoculation was sufficient to produce infection in over 99% of their experiments. In the average case a macule appeared at the site of inoculation after three weeks and gradually developed into a slightly scaly, purplish papule with an infiltrated base: in six months the lesion was as large as a "coffee bean." In half the cases ulceration occurred after six to eight months, and the untreated ulcers took nine months to a year to heal. Ulceration was thought to result from incidental traumatisation of the lesion. These observations correspond closely to the patient's account of the development of the vulvar lesion in the case described here. The incubation period in her case cannot be estimated. Manson-Bahr (1954) mentioned that the incubation period of oriental sore is variously stated in days, weeks, or months; periods of three years (Smith 1955) and three and a half years (Fidler 1952) have also been recorded.

Two other methods of transmission deserve mention. Transplacental infection of the fœtus can occur (Hindle 1928, Banerji 1955); Low and Cooke (1926) described a case of congenital leishmaniasis in a child, born in Britain, whose mother had become infected while in India. Blood has also been the vehicle of infection in other circumstances. Chung et al. (1948) recorded the development of kala-azar nine months and ten months after two children had each had an intramuscular injection of 20 ml. of their mother's whole blood as a prophylactic against measles: the mother's infection by leishmania was recognised soon after she had given the blood. André et al. (1957) reported a case in France of visceral leishmaniasis in a baby who received at birth an exsanguination transfusion of blood from a donor who had leishmaniasis of the skin and lymph-nodes.

A case of accidental infection with *L. donovani*, in a laboratory worker, has been recorded (Terry et al. 1950). The finger which was infected had been bitten on several occasions by experimentally infected animals.

Other Cases

All the other four cases of leishmanial infection which I have seen during the past five years presented as typical examples of so-called oriental sores. The lesion was solitary in each case.

Two of the patients were children from Cyprus—both were at school in England when the diagnosis was made, but in each case the lesion, which was on the forehead, had already begun to appear when the child left home, six months and eight months earlier. The boys came from different parts of the island; one was Greek and the other Turkish.

In the third case there was also presumptive evidence that the infection was contracted in Cyprus. The patient was a doctor who spent nine months in the island; he had never been elsewhere abroad, and he had travelled to and from Cyprus without stopping en route. His lesion was on the back of one hand and first appeared as a macule about five months after his return to England.

The fourth patient was a young woman who had never been out of England until she went on a bicycle trip to the South of France, where she spent five days camping in the Languedoc not far from Montpellier. She was away from home for altogether fourteen days. Her leishmanial granuloma was on one knee and was first noticed as a little pimple-like lesion five weeks after she left France: ulceration followed within ten days. Autochthonous cases of cutaneous leishmaniasis in southern France have been reported on a number of occasions (Rimbaud et al. 1958).

Diagnosis was made by biopsy in each of these cases

and confirmed by examining films of fluid obtained from the lesion. Cultivation was not attempted. Each patient was given a course of injections of one or another of the quinquevalent antimony preparations which are in current use. The lesions healed satisfactorily, except for the usual residual scarring.

Summary

A case of cutaneous leishmaniasis occurring in Britain and resulting from marital intercourse is reported.

The lesion, on the vulva, was at first mistaken for a primary syphilitic chancre. The correct diagnosis was made by biopsy. The patient's husband was found to have a symptomless recurrence of visceral leishmaniasis, which he had contracted in north-eastern Africa fourteen years earlier. Transmission of leishmanial infection by contagion is extremely rare.

Four typical examples of so-called oriental sore were seen in Britain during the past five years. In three cases the infection was contracted in Cyprus, and in the fourth case in the South of France.

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PREVENTION OF MIGRAINE IN CHILDREN BY PROCHLORPERAZINE

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A DOUBLE-BLIND trial is a satisfactory way of assessing the value of a drug in a condition of such varying severity as migraine. In view of the claims made for the value of prochlorperazine (' Stemetil ') in the prevention of migraine (Leyton 1957, Schaefer 1959) we have conducted a double blind trial in order to assess its value.

Method and Material

Selection of Cases

All children were seen by us at the Children's Hospital, Sheffield, or the Rotherham and Mexborough Hospitals and county pædiatric clinics. All had the classical picture of migraine, with a family history of the same complaint. Children with headaches alone, without the associated symptoms, were excluded. Only those who had had frequent attacks over a long period, not less often than about once a month, were included.

The double-blind method was adopted. The makers of the drug kindly supplied placebo, or control, tablets. Having made the diagnosis we prescribed the drug; and the pharmacist, by random sampling, supplied either the active drug or the control. When we saw the child again and repeated the prescription, the pharmacist supplied the opposite of that supplied previously. Only after we had studied enough patients and tabulated the results based on the parents' opinion did we receive the code which indicated the order in which the active tablet and the control tablet were prescribed.

We used a simple scoring method before receiving the code. This consisted of -3 to $+3$. -3 would mean that the patient was much worse. $+3$ would mean that he was much better. $+2$ meant that he was " better ". $+1$ meant that he was slightly better.

32 patients were studied; but some failed to come a second time, so the change-over of drugs could not be effected. 28 patients received the active drug, and 29 received the control.

The dosage was that recommended by the makers. This was $2^1/_2$ mg. twice a day for children $2^1/_2$ years of age, 5 mg. b.d. at the age of 5 years, and $7^1/_2$ mg. b.d. at the age of 10 years.

Results

The 28 patients receiving the active drug scored $+39$ (see table). The 29 patients receiving the placebo scored $+43$.

SCORES ALLOTTED ON THE ACTIVE AND CONTROL TABLETS

Score	No. achieving score	
	Control tablet	Active drug
+3	8	6
+2	8	9
+1	5	4
0	7	8
−1	1	1
−2	0	0
−3	0	0

It will be seen that there was no difference between the two groups. The placebo relieved many of the children.

There were no toxic effects. One mother said that the medicine made her child sick; the offending material was the inert tablet.

Summary

In a double-blind trial of prochlorperazine for the prevention of migraine in children, the drug proved no more effective than an inert control tablet. The inert tablet relieved many children of their attacks.

In the dosage used, prochlorperazine was not of value in the prevention of migraine in children.

Our thanks are due to Miss C. I. Crawford, chief pharmacist, for her help in this experiment; and to Messrs. May and Baker for supplying the tablets and control material, and for their advice and help.

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" . . . We all know . . . that it is usually possible to single one out of a vast array of possibilities by asking ' Yes or no ? ' only twenty times. A chromosome is able, so to speak, to answer such a yes-or-no question some two hundred million times, which corresponds to the total information stored in about one thousand large textbooks."—WARREN WEAVER *in* the Rockefeller Foundation annual report, 1958; p. 87.

SUBARACHNOID HÆMORRHAGE IN THE ARMY

1950-1956

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IN many reported series of subarachnoid hæmorrhage there are factors of selection for which allowance cannot be made. Necropsy studies can never be representative, and series from general hospitals often exclude patients who die suddenly or in the first few hours after admission. Neurosurgical series are usually biased by exclusion of these early deaths, or by inclusion of patients solely because of recurrent hæmorrhage. This study is an attempt to define more accurately certain features of the acute stage of subarachnoid hæmorrhage in young adults; for it is against this background that the results of neurosurgery must be set.

Method of Investigation

We have reviewed the records of all Army patients diagnosed during the seven years 1950–56 as having spontaneous intracranial hæmorrhage, intracranial aneurysm, or angioma. Hæmorrhage secondary to blood-disease or tumour was not included. 10 cases were rejected—5 because of insufficient evidence of subarachnoid hæmorrhage, 2 because there was no recent hæmorrhage, 2 because of inadequate clinical records, and 1 as a case of hypertensive cerebral hæmorrhage in a man over fifty-five years of age. 103 cases remained. The presence of subarachnoid hæmorrhage was proved by examination of the cerebrospinal fluid in 68 cases, by necropsy in 15, and by both in 20. All but a very few cases were followed for eight weeks from the onset of the illness. This period alone—the acute stage—will be considered here.

Classification of Cases

There is good evidence (Walton 1956, and others) that the prognosis in subarachnoid hæmorrhage is closely related to certain features of the early stages of the illness. Our cases were assessed according to their state on first admission to hospital, by applying the classification of Smith and Vollum (1956) for tuberculous meningitis:

Group 1 includes those who were fully conscious and rational, with no abnormal neurological signs beyond those of meningeal irritation.

Group 3 includes all patients who were comatose or completely inaccessible, or who had a complete hemiplegia.

Group 2 is intermediate, and includes those with abnormal neurological signs (excluding complete hemiplegia), and those who, despite alteration of consciousness, could still communicate with the examiner.

Group 4 comprises all patients who died before admission to hospital. These are included to complete the natural history of a condition which is one of the commoner causes of sudden death in young adults.

The course of the illness was classified according to a modification of a scheme proposed by Holmes (1957).

TABLE III—RELATION OF CLINICAL GROUP TO COURSE OF ILLNESS

Course	Death			Recovery		Total
	Deterioration		Recurrence		Steady recovery	
	Rapid*	Slow	Fatal	Non-fatal		
Clinical group 1 ..	3 (5·5%)	2	7	4	32	48
" " 2 ..	1	3	1	2	18	25
" " 3 ..	7 (35%)	1	4	1	7	20
Total ..	11	6	12	7	57	93

* All 10 patients in group 4 showed rapid fatal deterioration.

The course may be one of deterioration, either rapid (with death within forty-eight hours) or slow (with death within fourteen days), without evidence of further hæmorrhage; or initial improvement may be followed by recurrent bleeding, fatal or non-fatal; or recovery may be steady and uninterrupted.

Results

Of the 103 cases, 79 were first admitted to military hospitals (43 overseas, 36 in the United Kingdom) and 24 to civilian hospitals (1 overseas, 23 in the United Kingdom). 84 patients were admitted on the first day of the illness, 8 on the second, 4 on the third, 6 on the fourth to sixth days, and 1 (a case of so-called " pseudo-tumour syndrome ") in the third week.

Table I shows the cases grouped according to age, and the average incidence per 1000 at risk per year. The incidence rises steadily with age, and is four times as great at ages over forty-five as at under twenty, although the number in the former group is small.

Table II shows the distribution of cases by age in each clinical group, and the mortality in the first eight weeks. Mortality increases with age, and is significantly greater over the age of thirty (63%) than under (27%). (Here, and later, significance is taken at the 1% level.) The proportion of cases in group 4 is higher among the older patients, and the mortality is higher, irrespective of the initial clinical state, compared with the younger age-group.

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TABLE I—AGE-INCIDENCE

Age (yr.) ..	18–19	20–24	25–29	30–34	35–39	40–44	45–49	50+	Total
No. of cases ..	31	35	7	9	10	5	5	1	103
Average annual incidence per 1000 at risk ..	0·03	0·04	0·05		0·07		0·12		0·04

TABLE II—MORTALITY BY AGE AND CLINICAL GROUP

Age (yr.) ..	18–19	20–24	25–29	30–34	35–39	40–44	45–49	50+	Total under 30	Total over 30	Total
Clinical group 1 ..	2/16	3/15	0/3	1/4	3/5	0/1	2/3	1/1	9/55 (16%)	8/18 (44%)	17/73 (23%)
" " 2 ..	3/7	1/13	0/1	—	0/2	1/1	0/1	—			
" " 3 ..	4/7	0/4	2/2	2/3	1/1	2/2	1/1	—	6/13	6/7	12/20 (60%)
" " 4 ..	1/1	3/3	1/1	2/2	2/2	1/1	—	—	5/5	5/5	10/10
Total ..	10/31	7/35	3/7	5/9	6/10	4/5	3/5	1/1	20/73 (27%)	19/30 (63%)	39/103 (38%)

TABLE IV—RELATION OF RECURRENCE AND DEATH TO LENGTH OF ILLNESS

Week after onset	1					2			3	4	5+
Day after onset	1	2	3	4	5	6–8	9–11	12–14	15–21	22–28	29+
Patients at risk	103	88	82	82	79	78	78	77	73	70	66
No. of deaths..	15	6	0	3	1	0	1	4	3	4	2
Deaths (% per day).. ..	14·6	6·8	0	3·7	1·2	0	0·4	1·8	0·6	0·8	—
No. of recurrences ..	—	—	—	2	0	1	2	2	5	1	5
Recurrences (% per day) ..	—	—	—	2·5	0	0·4	0·8	0·9	1·0	0·8	—

Table III shows that the significantly greater death-rate among cases in group 3 (60%, as against 23% in groups 1 and 2 together) is due to many more deaths in the first forty-eight hours of the illness. The condition of 35% of cases in group 3 deteriorated rapidly, but this is true of only 5·5% of cases in groups 1 and 2. The recurrence-rate is 38% in group 3, and 20% in groups 1 and 2 combined, a difference which is not significant. Recurrent bleeding carries a higher mortality than the first hæmorrhage: 12 of 19 recurrences were fatal, as against 27 of 103 first hæmorrhages. The mortality of recurrent bleeding is also greater in group 3 (80%) than in groups 1 and 2 combined (57%).

The distribution of deaths and recurrences over the first eight weeks of the illness is shown in table IV. Death is common in the first five days, but uncommon thereafter. Recurrences after the first few days are at a steady rate.

Of 58 patients transferred to other hospitals after first admission, 32 were transferred in the first four weeks—9 by air and 23 by road. 1 patient's condition deteriorated during flight, perhaps because of heavy sedation. 2 other cases, transferred after the first four weeks, also became worse in transit; in both there was probably mild recurrent bleeding. In no other case did transport in the acute stage appear to aggravate the patient's condition, despite the long and often arduous journeys undertaken.

47 of the 58 patients transferred to neurological units underwent bilateral carotid angiography. 24 angiograms were abnormal. Of the 11 remaining patients 2 died and were found at necropsy to have intracranial aneurysms. Of the angiographic abnormalities 15 were aneurysms, 6 angiomata, and 3 of uncertain nature. Thus carotid angiography showed a probable source of bleeding in only 44% of cases investigated.

Discussion

In general our findings agree with those of others. The incidence of subarachnoid hæmorrhage is found to increase with age, at least up to sixty (Helpern and Rabson 1950, Walton 1956). Although the Service population, from which our cases are drawn, is highly selected by exclusion of the physically unfit, such selection is unlikely to operate against subarachnoid hæmorrhage (the cause of which is usually latent), except for a few cases with migraine and epilepsy. We therefore regard the annual incidence given in table I as approximately that in the population of the United Kingdom.

That mortality increases with age (Richardson and Hyland 1941, Walton 1956) can be shown even below the age of thirty (table II). The figure of 27% for the death-rate of our patients under thirty may be compared with figures of 31% (Richardson and Hyland 1941) and 27% (Walton 1956), although neither of these series included cases dead on admission. Our figure of 63% mortality for patients over thirty is higher than that given by others, but is based on small numbers.

Despite the differences in underlying pathology, clinical grouping derived from that used for tuberculous meningitis can be applied satisfactorily to subarachnoid hæmorrhage, as our findings show. The general conclusion to be drawn from tables II and III is that, apart from age, the principal prognostic sign is the severity and duration of the disturbance of consciousness, rather than the presence or absence of focal neurological signs (unless there is complete hemiplegia). Thus, hæmorrhage sufficient to cause deep coma on admission carried a mortality of 35% in the first forty-eight hours whereas lesser hæmorrhages, whatever mental disturbance or neurological signs they produced, were fatal in only 5% in the same period. Although the incidence of recurrent hæmorrhage is the same in all cases if they survive forty-eight hours, the mortality-rate of recurrences is higher in those who have had severe initial hæmorrhage.

Magee (1943) showed that the peak incidence of recurrence is in the second to fourth week of illness. Others have confirmed this (see particularly McKissock and Walsh 1956). In our cases there were only 3 recurrences and 2 deaths between the fifth and eleventh days inclusive, and the highest incidence of fatal recurrence was between the twelfth and fourteenth days. If surgery is to prevent these recurrences, clearly it must be undertaken before the end of the second week. Although angiography is probably more hazardous (Falconer 1954) and less likely to disclose underlying aneurysms (Magladery 1955) if performed in the first few days of the illness than later, the need for information on which to plan surgery seems to justify its being undertaken early (McKissock and Walsh 1956).

A further group of patients for whom surgery may have something to offer is those whose condition deteriorates slowly (Holmes 1957). In Holmes' series (of 100 cases in all) 23 of 43 patients died in this way, but in our series only 6 of 29. The reason for this difference is not clear, but possibly in Holmes' older patients more deaths were due to the sequelæ of prolonged unconsciousness (such as bronchopneumonia) and to the metabolic effects of brain damage.

Even in the most favourable situation—that of a mild hæmorrhage in a fit young man—the mortality is 16% in the first eight weeks. Of these deaths half should be preventable as they are due to recurrence or to slow deterioration. The angiographic demonstration of lesions in less than 50% of cases is disappointing, but recent advances in technique may make a higher rate possible.

If early surgery is to be contemplated, early transfer to a specialist centre is imperative. Henson (1957) thinks that after the first three or four days there is no undue risk in transporting these patients. Our findings do not contradict this view. In particular, transport by air, involving two road journeys of up to 50 miles, does not appear hazardous. The use of helicopters will make transport by air easier and quicker, and we suggest that this method will be safer for anything more than a short road journey.

Summary

The natural history of 103 cases of spontaneous subarachnoid hæmorrhage in Army patients in the years 1950–56 is described.

The incidence and mortality rose steadily with age. Death was commoner in the first five days than later. Recurrent bleeding occurred at a steady rate after the

first few days. Recurrences carried a higher mortality than the first hæmorrhage.

When the cases were classified clinically in terms of the severity of the initial hæmorrhage, the death-rate was found to be significantly greater among those who were comatose or completely inaccessible, or who had a complete hemiplegia. The severity and duration of the disturbance of consciousness was the most reliable prognostic sign.

To prevent recurrences, surgery, and therefore angiography, should be undertaken before the end of the second week. Unfortunately angiograms showed the probable source of bleeding in less than half of those so investigated. Transporting the patients in the acute stage did not aggravate their condition.

We should like to thank Dr. Honor Smith, Mr. W. S. Lewin, Dr. C. W. M. Whitty, and Dr. R. G. Willison for advice and criticism and the statistical division of the Army Medical Directorate for their invaluable help with the case-records.

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SURVIVAL IN AN AFIBRINOGENÆMIC SUBJECT OF FIBRINOGEN PREPARED FROM "TIME-EXPIRED" BLOOD

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THE rising clinical demand for the fibrinogen-containing fraction of human plasma would be difficult to meet entirely with material prepared from freshly drawn blood. On the other hand, relatively large quantities are recoverable from the plasma of stored blood, rejected for transfusion when the expiry date of the red cells has been passed. The physical properties of the fibrinogen fraction from such blood differ slightly from those of freshly collected blood, and we have therefore observed the survival of the former fraction in the circulation of a young woman with afibrinogenæmia.

Material and Methods

The Patient

In this case, previously described in detail (Pinniger and Prunty 1946, Hardisty and Pinniger 1956) the hæmostatic mechanism is normal except that the plasma forms no clot whatever, although a small, flocculent precipitate (corresponding on different occasions to 30–100 mg. protein per 100 ml.) has repeatedly been observed to form after incubating recalcified citrated or oxalated plasma for an hour or more. In one test the nitrogen content of this precipitate indicated that less than one third of its weight was attributable to protein. The patient's platelet count runs at about 600,000 per c.mm. blood (normal 150,000–350,000 per c.mm. blood).

Preparation of Fibrinogen from Plasma of "Time-expired" Blood

The method of Kekwick, Mackay, and Record (Kekwick and Mackay 1954) was adapted for plasma from "time-expired" blood (i.e., 21 days or more old) intended also for γ-globulin fractionation. The fibrinogen fraction settles less readily from old plasma by the original method, and contains a high proportion of insoluble matter.

For the preparation, all reagents and vessels are sterilised. A pool of 60 litres of sterile plasma is prepared from 30–40 "ten-donor" pools selected visually for low fat content, diluted with an equal volume of water and cooled to 0°C. To it are slowly added 13·2 litres of diethyl ether, keeping the temperature between 0°C and −1°C and stirring until the ether has completely dissolved. The mixture stands overnight at 0°C. On the following day the clear supernatant is removed and the sludge containing the precipitated fibrinogen is centrifuged at 0°C. The precipitate obtained is suspended in 12 litres of a solution containing 80 ml. per litre of ether dissolved in 0·15*M* sodium-chloride, 0·0125*M* trisodium-citrate solution, centrifuged again, and the supernatant discarded. The precipitate is re-dissolved in 6 litres of 0·3*M* sodium-chloride, 0·0125*M* trisodium-citrate solution. Warming in a water bath at 37°C accelerates dissolving. Fine particulate matter is removed by filtration in three stages through: (1) 'Hyflo-Supercel': 300 ml. loose powder per litre solution on a Ford CCNA pad (cellulose: 70 sq. cm. per litre solution); (2) Ford FCB pad (asbestos and cellulose: 70 sq. cm. per litre solution); (3) Carlson EK pad (asbestos and cellulose: 140 sq. cm. per litre solution).

The final solution is bottled, spun-frozen without delay, and dried. This fibrinogen solution contains between 1·5 and 2 g. protein per 100 ml., of which 60–70% is clottable. The diagram obtained by moving-boundary electrophoresis very closely resembles that of the fibrinogen fraction from fresh plasma, suggesting that the lower clottability of this preparation is not attributable to any gross change in the molecular structure or to the inclusion of proteins of other mobilities in the fraction.

After incubation at 37°C for 16–24 hours, a sterile solution 0·2 g. per 100 ml. in citrate saline does not clot on addition of thrombin, indicating the presence of plasmin. Fibrinogen prepared from fresh undiluted plasma by the method of Kekwick, Mackay, and Record remains clottable for as long as 3 weeks under similar conditions. When diluted with an equal volume of water, however, both old and fresh plasma have a short fibrinogen "life" on incubation. The dilution of old plasma is necessary to induce more complete sedimentation of the fibrinogen precipitate. It will be pointed out below that this apparent disadvantage of the "time-expired" material does not impair its clinical usefulness.

For clinical use the product is freeze-dried in 3–4 g. quantities in blood-transfusion bottles and the contents are retrospectively estimated from the nitrogen value of a representative clot. The statements given below of the quantities administered clinically are derived from these determinations.

Administration of Fibrinogen Solution

The patient received two intravenous infusions, separated by an interval of 11 months.

At the first (batches 105, 107, 110) she was given 13·8 g. dissolved in 450 ml. water immediately before a dental extraction. Postoperative hæmostasis was achieved within a few hours, as in a normal person, by contrast with the oozing of some days' duration which previously followed tooth extractions in this patient when blood or a blood derivative had not been given.

At the second infusion (batches 114, 115), the patient received 17·6 g. in 460 ml. water a week before the expected date of a menstrual period, because over the previous four months, immediately following her marriage, menorrhagia had been troublesome. The subsequent period occurred a few days later than expected and was very light. The plasma-fibrinogen concentration lay between 0·04 and 0·06 g. per 100 ml. during the menstrual period. Subsequent menstrual periods have not been unduly heavy.

Estimation of Fibrinogen Concentration in Plasma

After the first infusion, plasma samples were estimated by one or more of three methods:

1. Oxalated plasma was recalcified and allowed to form a clot which was removed after 1–18 hours, and fibrin was determined as N by the micro-Kjeldahl technique.

2. Citrated plasma was recalcified and allowed to form a clot which was removed after 10–15 minutes and the fibrin determined gravimetrically (Ingram 1952). The appearances of the clot obtained in this method were those of purified fibrinogen rather than of normal plasma. Experiments in vitro confirmed that, when time-expired fibrinogen was added to the patient's plasma, fibrin could be recovered as fully as from saline solution.

3. Serial dilutions of citrated plasma were incubated with coagulase-positive *Staphylococcus aureus* and the highest dilution in which clumping occurred was noted (Duthie 1954). The method was calibrated by parallel determinations on a plasma whose fibrinogen concentration had been measured by method 2.

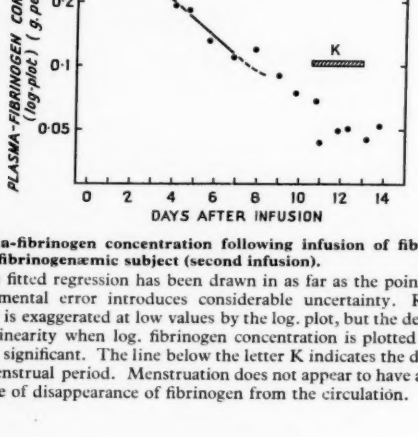
After the second infusion all samples were estimated by method 2.

Results

Since, in this patient, previous transfusions had seriously disorganised the superficial arm veins, only rather small samples of blood could be obtained, and some were lost through clotting in the syringe. For the same reason, it was not thought practicable to estimate her blood-volume directly; so a tentative figure for the plasma-volume was derived from the body-weight and the venous hæmatocrit.

First infusion.—By the three methods of determination, five samples over 12 days yielded ten estimates. There was no evidence of systematic differences between the methods of estimation; and fibrinogen concentration appeared to regress exponentially against time. The pooled results from the three methods yielded a rate (with standard error) for the disappearance of the fibrinogen from the patient's circulating plasma of 14·3 (±1·9) % per day. From the regression curve, the fibrinogen concentration at time $t=0$ was 0·31 (±0·01) g. per 100 ml. plasma, which was only some 57% of the expected concentration which had been calculated from the supposed plasma-volume, but was very near the observed plasma concentration—0·28 g. per 100 ml.—15 minutes after the end of the infusion. This was regarded as a preliminary experiment, mainly confirming the comparability of the three methods of estimation.

Second infusion.—Eighteen samples were obtained over 14 days and estimated by method 2 (see figure). A regression empirically fitted to the results in the form



Plasma-fibrinogen concentration following infusion of fibrinogen in afibrinogenæmic subject (second infusion).

The fitted regression has been drawn in as far as the point where experimental error introduces considerable uncertainty. Random scatter is exaggerated at low values by the log. plot, but the departure from linearity when log. fibrinogen concentration is plotted against time is significant. The line below the letter K indicates the duration of a menstrual period. Menstruation does not appear to have affected the rate of disappearance of fibrinogen from the circulation.

$y=\alpha+\beta\rho^t$ (where y is the fibrinogen concentration at time t, α the asymptote; $(\alpha+\beta)$ the fibrinogen concentration at zero time, taken as 10 minutes after the start of the infusion; ρ the proportion of the fibrinogen remaining in the plasma after unit time, and t the time in days) indicated a plasma concentration 2 hours after the start of the infusion of 0·47 (±0·01) g. per 100 ml. This agrees well with the observed value of 0·48 g. per 100 ml. at that time and with the expected concentration of 0·43 g. per 100 ml., again calculated from the supposed plasma-volume.

Discussion

Two explanations are possible for the curvilinear relation between log. fibrinogen concentration and time, seen in the figure. Either the curve might be logarithmic but fall towards the asymptote of a low concentration always present, as in the fitted equation; or it might be the resultant of a superimposed series of movements of fibrinogen between the plasma and various extra-circulatory "pools". These explanations are not of course mutually exclusive, although the first seems unlikely because previous observations have failed to demonstrate fibrinogen in this patient's blood except after infusions; nor can the flocculent precipitate previously referred to have contributed to the "asymptotic" low concentration, because it would have taken longer to appear than the time allowed for harvesting the fibrin in this experiment. If the second explanation is accepted, the early, rapidly falling portion of the curve could be attributed to the initial stages of equilibration with extravascular fluid, when movement outwards from the plasma is rapid, and the later portion would principally reflect metabolic removal, at a rate masked in the earlier stages. It is the slope of this later portion from which the rate of turnover has generally been derived, although of course a rate calculated directly from this slope might include a component representing back-diffusion from an extravascular pool. The rate so derived from the tail of the regression of our second experiment is approximately 15% per day: the line so fitted, when extrapolated back to zero time, cuts the ordinate at 0·33 g. per 100 ml., which represents some two-thirds of the dose injected. The separation of these complex effects requires more work, and the problem is being further studied.

Meanwhile two points of interest emerge:

First, it is curious that our preliminary experiment did not detect the early phase of rapid removal from the bloodstream, although otherwise our results are very similar to those obtained from a comparable infusion given to an afibrinogenæmic boy by Gitlin and Borges (1953): rapid loss of about half the injected fibrinogen was clearly demonstrated during the first 2 days. It is hardly conceivable that 5·9 g. (43% of 13·8 g.), representing a clearance of 1·9 litres of plasma (9/20 of the assumed plasma-volume) can have been sequestered at the tooth socket in the achievement of hæmostasis (although Fitzgerald and Jackson [1956] obtained the astonishing figure of 63 g. of fibrin from a retroplacental clot). It also seems unlikely that our findings could be explained by temporary fibrinogenolytic activity, happening to destroy 43% of what was administered, since one would expect to see evidence of equilibration after a short-lived fibrinogenolysis had passed off.

On the other hand, in our second infusion, the initial equilibration seems to have occupied at least 4 days, in as much as after this point the observations can be fitted to a straight line on the log. plot. Perhaps there is great variability in the duration of the early phase of the curve in such subjects, and possibly in our first infusion this phase was already completed by the time of our first blood sample 15 minutes after the completion of the infusion.

ESTIMATES OF RATES OF UTILISATION OF FIBRINOGEN IN MAN

Source	Subject(s)	Technique	Mean rate of disappearance of specific activity or material (% per diem)
Madden and Gould (1952)	Normal	Test subjects fed ^{35}S	12
Volwiler et al. (1955)	,,	Donor subjects fed ^{35}S	17
Christensen (1958)	,,	^{131}I-labelled	15
Gitlin and Borges (1953)	Afibrinogenæmic	(1) Normal fibrinogen infused	16
		(2) Ultraviolet-irradiated fibrinogen infused	20
Frick and McQuarrie (1954)	,,	Fraction I infused	24
Present case	,,	"Time-expired" fibrinogen infused	(1) 14 (2) *ca.* 15

In normal subjects the values were derived from measurements of radioactivity; whereas in the afibrinogenæmic subjects fibrinogen was assayed by chemical or immunological methods or with coagulase. The cited rates are obtained from the slow, late exponential portions of the published curves, after the initial, rapid equilibration phase was completed. The mean of all the quoted values is about 17% per day, and the mean of the three rates derived from normal subjects is about 15% per day. For purposes of numerical comparison with other work in which the conception of $^1/_2$-survival time has been employed, these mean values may be expressed as $^1/_2$-survival times of about 3·8 and 4·3 days respectively.

The *second point* is the survival of our material in the circulation of this patient. The accompanying table gives a series of values derived, as explained above, from the later, slow portion of the curve, obtained from published studies of the turnover of fibrinogen in normal and afibrinogenæmic subjects; it is apparent that our values are near their mean (17% per day). This suggests that fibrinogen prepared from time-expired blood is not destroyed more rapidly in the body than material prepared from fresh blood and may therefore be accepted as an effective substitute for it. It thus seems reasonable to suppose that the plasmin contaminant of the fibrinogen preparation, demonstrated in vitro, is inactivated by the antiplasmin in the recipient's plasma.

In this report we have not employed the conventional terminology of half-survival time, because we feel that the term should be reserved for strictly one-component, first-order changes, such as the decay of radioactivity. Processes which are really more complex, but which are found to approximate to an exponential for a given period of observation, cannot logically be considered in terms which imply a steady logarithmic change over an indefinite time. We have therefore expressed rates of change as percentages removed from the circulation per day during the periods in which observations were being made.

Summary

A method of preparing fibrinogen from the plasma of "time-expired" blood is described.

This fibrinogen was twice transfused into a young woman with afibrinogenæmia. On one occasion a tooth was extracted and normal hæmostasis was achieved. As has been reported with other preparations, about a third to half of the injected dose was rapidly lost from the circulation, but the remainder disappeared more slowly at about 15% per day.

This value, which compares well with those obtained in other ways, probably represents the normal rate of turnover of this protein. Fibrinogen prepared from "time-expired" blood thus seems likely to be of similar clinical value to that obtained from fresh blood.

Our thanks are due to Dr. C. A. Foster for his help with the infusions and with the venepunctures; to Dr. N. P. L. Wildy for performing the coagulase tests; to Dr. G. Bartsch, of the Medical Research Council's Statistical Research Unit, for the statistical analysis of the second regression; and to Dr. W. d'A. Maycock for valuable discussion and criticism.

(*References at foot of next column*)

EXACERBATIONS OF CHRONIC BRONCHITIS TREATMENT WITH OXYTETRACYCLINE

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EXACERBATIONS of chronic bronchitis are among the most common conditions presenting for treatment in general practice in Britain (Pemberton 1949, Fry 1954, Horder and Horder 1954, Logan and Cushion 1958). Until recently treatment was ineffective; but now, for the patient with severe chronic bronchitis, the value of long-term antibiotics in shortening attacks (May and Oswald 1956, Moyes and Kershaw 1957, Buchanan et al. 1958) and in preventing them (Edwards et al. 1957, Buchanan et al. 1958, Edwards and Fear 1958) is reasonably well established. The evidence in favour of treating exacerbations with short courses of antibiotics is less conclusive (Elmes et al. 1957).

Chronic bronchitis is gradual in its onset. In the early stages the patient usually enjoys good health punctuated by "chesty colds". Later on repeated attacks lead to a permanent loss of respiratory function which may remain moderate or may proceed, with exacerbations, to respiratory failure and death. In general practice, patients may come for treatment at any stage of this process, and in the cases where permanent respiratory symptoms are moderate or slight the precise indications for antibiotic treatment are far from clear.

The Present Investigation

The investigation reported here was a double-blind controlled trial of antibiotic treatment of exacerbations of chronic bronchitis which were mild or only moderately severe. In planning the trial, and during the preliminary pilot studies, it was apparent that in severely ill patients the use of control treatments would be ethically indefensible. It was not, however, possible to devise a method of assessing severity which could be uniformly applied by all the doctors participating. Accordingly the practitioner was asked to classify his cases, on his own judgment, as:

A. Antibiotic necessary.
B. Intermediate.
C. Antibiotic unnecessary.

Patients in group A were treated as the doctor thought

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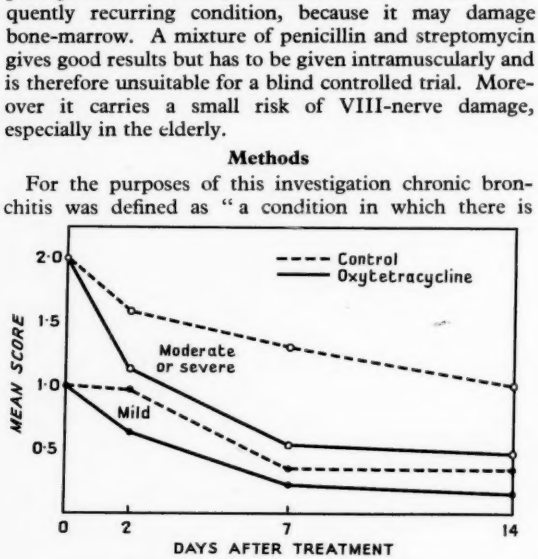
fit, the controlled trial being confined to groups B and C. In this way no patient entered the trial if his doctor felt that antibiotic treatment was imperative.

The antibiotic selected for trial was oxytetracycline, a drug active against the common pathogens in chronic bronchitis (Flint 1954, Gabrielson et al. 1954, Helm et al. 1954) and, at least under general-practice conditions, free from serious side-effects. Chloramphenicol, while perhaps more effective, is unsuitable for use in a frequently recurring condition, because it may damage bone-marrow. A mixture of penicillin and streptomycin gives good results but has to be given intramuscularly and is therefore unsuitable for a blind controlled trial. Moreover it carries a small risk of VIII-nerve damage, especially in the elderly.

Methods

For the purposes of this investigation chronic bronchitis was defined as "a condition in which there is persistent or recurrent cough with diffuse physical signs in the chest, in which X-ray has excluded other disease" A patient was held to be suffering from an exacerbation when there had been "a sudden worsening (during the past week) characterised by one or more of the following symptoms: increased cough, increased volume of sputum, increased purulence of sputum, increased breathlessness or fever". The "baseline" severity of each patient's bronchitis was indicated by his exercise tolerance during the previous summer, according to the following grades:



Response of treated and control groups.

Grade 2.—Able to walk with normal people of own age on level, but unable to keep up on hills or on hurrying because of breathlessness. Able to do all housework, but breathless on digging for more than short periods and carrying loads (e.g., coal) upstairs.

Grade 3.—Unable to keep up with fit people walking on the level. Able to walk at least one mile flat and to climb a flight of twelve stairs without distress and to perform light household duties.

Grade 4.—Unable to walk more than 300 yards without pause for breath. Able to do sedentary work and the lightest household jobs.

Grade 5.—Breathless on walking a few yards or on undressing.

The severity of the exacerbation was assessed at first presentation, and after 48 hours, 7 days, and 14 days, on a four-point scale, as follows: 0, patient's baseline; 1, mild attack; 2, moderate attack; 3, severe attack. More objective criteria of severity proved impracticable. In some cases intermediate scores (0·5, 1·5, &c.) were employed.

In addition to recording the severity of the patient's bronchitis, and of the exacerbation, a record was also made of the patient's age and sex and of the presence or absence of the following features of the exacerbation: increased cough, increased sputum, increased purulence of sputum, increased dyspnœa, and fever. Sputum was sent for culture after the first consultation and after the completion of treatment—all bacteriology being carried out at the same laboratory.

TABLE I—CHARACTERISTICS OF THE TREATED AND CONTROL GROUPS

—	Oxytetracycline	Control
Total cases	26	27
Classification at presentation:		
B	15	16
C	11	11
Age:		
Less than 45	4	7
45–54	6	3
55–64	5	7
65–74	10	7
75 and over	1	3
Sex:		
Male	15	16
Female	10	11
Not recorded	1	0
Symptoms:		
More cough	26	24
More sputum	21	23
More purulence	16	16
More dyspnœa	23	22
Fever	6	6
Category previous summer:		
Grade 2	17	15
„ 3	6	8
„ 4–5	3	3
Not known	0	1
Organisms present in sputum at onset:		
Pneumococcus	6	6
Influenza bacillus	6	6
Streptococcus	2	7
Other	2	1
Nil	10	7

As explained above, a patient presenting with an exacerbation of bronchitis was initially assigned by the doctor to one of three categories: (A) antibiotic necessary, (B) intermediate, or (C) antibiotic unnecessary. Patients in category A were not included in the trial but record cards were completed for them. Patients in category B and C were provided with a course of capsules, containing either oxytetracycline (given in the dosage 250 mg. q.i.d. for 5 days) or lactose. The practitioners each had a series of numbered bottles containing either oxytetracycline or lactose, arranged in random order, the key to the numbers being in the possession of another member of the group. All the patients were given oral vitamin B and expectorants, antispasmodics, and other treatment as indicated.

Results

Fifty-eight patients were placed in categories B and C and entered the trial. The records of two of these patients were inadequate, and in three other cases treatment was discontinued because of possible toxic effects from the tablets (two were on oxytetracycline and one on control tablets). In addition, records were kept of eleven cases in category A.

TABLE II—PROGRESS OF TREATED AND CONTROL PATIENTS CLASSIFIED ACCORDING TO THE SEVERITY OF THE EXACERBATIONS

—	Total	Failures	Mean severity score on day: 1	2	7	14
Mild attack:						
Oxytetracycline	11	0	1·00	0·64	0·23	0·14
Control	13	1	0·96	0·96	0·32	0·31
Significance			N.S.	N.S.	N.S.	N.S.
Moderate/severe attack:						
Oxytetracycline	15	0	2·03	1·13	0·53	0·47
Control	14	4	2·04	1·57	1·36	1·00
Significance			N.S.	5%	5%	N.S.

N.S., not significant.

Table I shows that the treated and control groups were very similar in composition. For the purpose of analysis the patients were further divided according to the severity at onset, cases scoring 1 being regarded as mild and those over 1 as moderate-to-severe. At assessments after the first, the withdrawal of the patient from the trial because of poor progress was recorded as a failure and scored 4 points.

The response of the treated and control groups is recorded in table II and in the figure. In both the mild and the moderate-to-severe groups the treated patients did better than the controls. In the mild cases this difference was not significant, but in the moderate-to-severe group it was significant at 2 and 7 days.* By 2 days fourteen treated patients were improving compared with only seven control patients; one control had been withdrawn from the trial and put on other treatment. After 1 week, seven treated patients had returned to their base-line condition whereas only 1 control had done so and two further control cases had been withdrawn. By 14 days the advantage of the treated patients ceased to be significant, but a fourth control patient had required alternative treatment.

TABLE III—CHARACTERISTICS OF PATIENTS IN CATEGORIES A, B, AND C

—	A	B	C
Total number	11	31	22
Age:			
Under 45	1	6	5
45–54	2	3	6
55–64	2	7	5
65–74	3	12	5
Over 75	2	3	1
Not known	1	0	0
Category last summer:			
Grade 2	4	15	17
„ 3	3	11	3
„ 4–5	4	4	2
Not known	0	1	..
Symptoms of exacerbation:			
Fever	8	9	3
More purulence	11	20	12
Severity of exacerbation at onset:			
1	3	8	16
2	3	22	5
3	5	1	1

Further analysis shows that the advantage of the treated over the control patients was largely confined to the patients in category B (intermediate). In fact there is a close correlation between the initial assessment of severity and the classification into categories B and C. The advantage of treated patients over controls applied irrespective of whether any organism was cultured or not.

The eleven patients in group A, who remained outside the trial, were treated with various antibiotics. Two of them died.

Discussion

Our results show that, even where antibiotic treatment is not considered essential, a patient with an exacerbation of bronchitis may derive measurable benefit from it—at any rate if the attack is more than mild.

The criteria on which patients were assigned to category A, B, or C, and on which they were graded for severity, are likely to have varied between participating doctors. Table III compares the features of the patients in groups A, B, and C, and suggests that the decision to give antibiotics was based on the patient's greater age, on the severity of the bronchitis and of the exacerbation, and on the presence of fever and purulent sputum.

* Significance is calculated by the method of Armitage (1955) from the actual score distributions. This takes into account the non-metrical nature of the scores.

Summary

A double-blind controlled trial of oxytetracycline in mild or moderately severe exacerbations of chronic bronchitis is described.

The trial was carried out by a group of general practitioners on a total of fifty-eight patients.

Treated patients recovered sooner and deteriorated less often than the controls. This advantage is statistically significant for patients with moderately severe attacks but not for those with mild attacks.

We are grateful to Messrs. Pfizer for a supply of oxytetracycline ('Terramycin') and dummy capsules, and for the advice of Dr. W. Williams. We are also indebted to Dr. C. M. Fletcher and Dr. N. C. Oswald for their helpful advice.

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PROLONGED TREATMENT WITH STEROIDS IN SEVERE CHRONIC ASTHMA

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CORTISONE and corticotrophin are known to be valuable in the treatment of status asthmaticus, but opinions differ as to their use in chronic asthma. Good results have been reported with prolonged treatment (Lowell et al. 1953, Savidge and Brocklebank 1954a, Davies and Williams 1955, Morrow Brown 1958). In contrast, the Medical Research Council (1956) found that the initial improvement in patients having cortisone, as compared with control patients, was not maintained. At the end of 6 months there was no significant difference between their two groups. Our findings are at such variance with those of the Medical Research Council that we wish to present the results of our own experience, for we consider these drugs to be of real value in severe chronic asthma.

The Trial

A group of fifty patients were treated with steroids for periods of 3 months to 5½ years (mean duration 2·7 years). There were thirty-three women and seventeen men, aged 23–66 (mean 47·2 years). All had severe chronic asthma, resistant to conventional treatments, and responding initially to steroids. Most had been unable to work or do their household duties for many months, and frequent hospital admissions had been necessary. The mean duration of asthma was 10·3 years.

Cortisone was given by mouth to thirty patients, most of

whom needed 50–75 mg. daily. Corticotrophin proved more effective in four cases, and sixteen of the later cases were treated with prednisone. Response to treatment was assessed by the frequency of paroxysmal dyspnœa, the capacity for exercise and work, and the degree of bronchospasm.

Results

Good results were obtained in thirty-nine of the fifty patients, and there was moderate improvement in five others. The results were poor in two women and one man with infective asthma associated with persistent purulent sputum, and three patients died during treatment. Twenty-one patients, previously unable to work, resumed their paid jobs or household duties.

Illustrative Case-reports

CASE 1.—A woman, aged 33, had had severe asthma for 14 years and had been admitted to hospital twelve times during this period. Severe bronchospasm persisted for half the year. She felt that her family was neglected. She improved within 2 days of starting treatment with cortisone, and for the past $5^1/_2$ years, while taking 25–37·5 mg. daily, she has remained almost free of asthma. She had a severe relapse 4 weeks after cortisone was stopped in a double-blind trial.

CASE 2.—A man, aged 64, had been subject to winter bronchitis with purulent sputum for 30 years. During the past 6 years increasingly severe paroxysmal dyspnœa had developed. He had been in hospital with asthma three times in the past year, and he was afraid to work. Cortisone was started in November, 1956. His condition improved rapidly, and he has since had only moderate bronchospasm for a few weeks each winter in association with infection. He has taken cortisone 25–50 mg. daily. He relapsed 2 weeks after cortisone was stopped in a double-blind trial.

CASE 3.—A woman, aged 60, who had had asthma for 21 years, had been forced to give up her light assembly work 6 years previously. She had been in hospital continuously for 2 years, having frequent injections of adrenaline and aminophylline. In the past $4^1/_2$ years, while taking cortisone 50–75 mg. daily, she has had only mild attacks of asthma, and she can now do all her own housework. She relapses when given control tablets.

Side-effects

Rapid weight gain, due both to improved appetite and to fluid retention, made it necessary to restrict many patients to a low-salt reducing diet. Cortisone had to be stopped in two patients because of severe depression. Hirsuties and a moon-face developed in three patients.

Deaths

Three patients died during treatment.

CASE 4.—A woman with asthma, aged 54, was treated for $3^1/_2$ years with cortisone or corticotrophin, and she showed moderate improvement. While in hospital with a relapse of asthma associated with bronchitis, she died of cerebral hæmorrhage. At no time was her blood-pressure raised. The suprarenal glands were macroscopically normal at necropsy.

CASE 5.—A woman, aged 41, had asthma which was treated with cortisone 75 mg. daily, with good result. She was then admitted to hospital with bronchitis, and cortisone was stopped. 7 days later severe asthma developed. Cortisone 100 mg. daily was restarted on the 11th day, but she did not respond, and she died in status asthmaticus on the 19th day. Necropsy showed macroscopically normal suprarenal glands.

CASE 6.—A man, aged 34, had severe congenital kyphoscoliosis with advanced emphysema and persistent bronchospasm. He had been unable to work for 3 years. In 1955 he was in hospital with severe congestive cardiac failure, and he responded very slowly to treatment. After discharge he remained cyanosed and dyspnœic on slight exertion, being able to walk slowly only about 200 yards. Treatment with prednisone was started in September, 1956. Within 2 days there was much improvement and the bronchospasm disappeared. The patient was able to resume clerical work and to dig his garden. After 4 months' treatment with cortisone he died at home of acute bronchitis. Necropsy was not performed.

Death in case 4 was unlikely to be related to treatment, although the cause of her cerebral hæmorrhage was obscure. In case 5 it was most unfortunate that cortisone was stopped on admission and restarted in inadequate dosage. The third patient (case 6) was an ill man before treatment, and his terminal bronchitis cannot reasonably be ascribed to prednisone.

Control Periods

In fourteen cases which were satisfactorily controlled on cortisone, inert tablets were substituted without the patients' knowledge. Of these, eight showed a definite relapse within a period of 2 months, two being admitted to hospital in status asthmaticus. The condition of five other patients deteriorated more gradually and one remained unchanged. Shortly after stopping treatment twelve other patients relapsed. These results encouraged us to undertake a double-blind trial, for it seemed important to provide more objective evidence of prolonged benefit from cortisone, even at the expense of distressing relapses.

Double-blind Trial

Eleven patients took part in the double-blind trial. A twelfth patient moved away from the district during the trial period. All were severe chronic asthmatics, who appeared to require a maintenance dose of cortisone. There were eight women and three men, with a mean age of 54 years. They were seen at 2–4-week intervals, when their symptoms and working capacity were noted. The degree of audible bronchospasm was assessed, and the 1-second forced expiratory volume ($F.E.V._1$) was recorded (Thomson and Hugh-Jones 1958).

During an initial observation period of 3–5 months (mean 18·6 weeks), the patients continued to have cortisone in the smallest dose which controlled their symptoms. This varied from 25 to 75 mg. daily. During the next 3 months half continued with cortisone, and the others took identical inert tablets. The change from cortisone to control tablets was gradual in order to avoid sudden withdrawal.

The standard 25 mg. cortisone tablets were replaced by tablets containing 17 mg. cortisone for the first control week, and 8 mg. for the second control week. Inert tablets were continued thereafter. Neither patient nor doctor knew whether cortisone or inert tablets were being dispensed.

If a patient relapsed, known cortisone was restarted and continued until the end of the 3-month period. The general practitioners knew of the trial and were warned to give cortisone if necessary. At the end of 3 months the patients changed from cortisone to inert tablets, and vice versa, for a further 3-month period.

Results

During the initial observation period there were minor relapses only. But during the period on unknown inert tablets, nine patients had moderate or severe recurrences of asthma, which kept them in bed and prevented work. Several of these relapses were of alarming severity.

CASE 1.—(See above.) This patient developed troublesome

asthma on the first day of a family holiday after 4 weeks of the control period. For a fortnight she was unable to leave the holiday cottage, apart from short drives when she was confined to the car, and she could do no housework. Her husband was most unsympathetic, and the couple were at loggerheads for weeks. She improved rapidly when known cortisone was again started by her doctor.

Two patients relapsed during the first fortnight, while the dose of cortisone was being reduced. Three patients relapsed at the end of the first fortnight, and the other four 3–5 weeks after starting the control period. Improvement was usually rapid after cortisone was resumed, though several patients were persistently more wheezy than usual for up to a month. One patient relapsed after 5 weeks of the unknown cortisone period and improved 3 days after restarting known cortisone. Another patient remained well throughout both parts of the trial.

The F.E.V.$_1$ readings were not helpful as a means of comparing the periods on cortisone and control tablets. Because patients often relapsed early in the 3-month periods cortisone was usually restarted by the general practitioner, and spirometry was not done at the time of relapse. In four patients, however, where comparable measurements were made in the two periods, the mean F.E.V.$_1$ during the cortisone period was 490 ml. and during the control period 380 ml. It is interesting that the mean F.E.V.$_1$ of the patient who relapsed while taking unknown cortisone was 480 ml., compared with 360 ml. during the control period in the other half of the trial.

Thus nine patients relapsed while taking unknown inert tablets, and one while taking unknown cortisone. The probability that this distribution of relapses was due to chance is 1 in 1000.

Discussion

Most of these severely disabled asthmatics showed considerable improvement with prolonged steroid treatment, and other workers have reported similar good results. Our double-blind trial shows more objectively that prolonged control of severe asthma is usually achieved with cortisone. It can be argued that prolonged treatment with cortisone merely suppresses the normal adrenal output. Relapse on withdrawing cortisone would then result from adrenal suppression. We tried to avoid such an acute withdrawal effect by gradual reduction of cortisone dosage.

There are features of the Medical Research Council trial which we venture to criticise and which may explain why prolonged benefit from cortisone was not demonstrated.

To consider first withdrawals from the trial groups, if we assume that most defaulters failed to continue treatment because of failure to benefit, we find that ten left the control group by reason of continuing asthma (five in status asthmaticus and four defaulters), while only four left the cortisone group (two in status asthmaticus and two defaulters). Thus it seems that the control group was gradually shorn of its severe asthmatics as the trial proceeded, and that cortisone was at a disadvantage in a group with more severe and persistent asthma. Cortisone was said to be ineffective after the first 8 weeks, but only two patients having cortisone (one in status asthmaticus and one defaulter) left the trial after 8 weeks by reason of asthma, while five (three in status asthmaticus and two defaulters) left the control group after 8 weeks.

The control patients had a higher mean "dose" of placebo (3·54 tablets per day) at the 3-month midpoint of the trial than the patients having cortisone (2·86 tablets per day). This larger number of tablets suggests that asthma was more troublesome in the control group. The cortisone group did, in fact, show some advantage at the end of the trial in exercise tolerance and working ability, and the clinicians taking part thought that twenty-three of the forty-nine patients improved during the trial whereas only twelve of the forty-seven control patients improved. Four of the five hospitals concerned were still using prolonged cortisone treatment for approximately two-thirds of both the control and the cortisone groups when they submitted their reports 6–22 months after the trial. Our trial, of course, is not strictly comparable to the Medical Research Council trial, in that they compared prolonged treatment with cortisone with prolonged treatment with a placebo, whereas we stopped cortisone treatment even in patients who were doing well on it.

It is important that an adequate amount of cortisone be given, for severe asthma returns in many patients if the dose falls below a critical level. We encourage patients to increase their dose if necessary, especially if a chest infection develops, provided always that they take the smallest effective amount. Short antibiotic courses are arranged for patients liable to recurrent chest infections. In time, many patients are able to reduce their dose of cortisone. Six patients have now stopped treatment altogether after long courses of cortisone, and seven require only intermittent treatment. The need for continued treatment should be reassessed periodically by the cautious use of control tablets, for patients are very liable to become dependent on cortisone.

The risks of prolonged treatment with steroids are well known, and a number of deaths have been reported during treatment (Savidge and Brocklebank 1954b), which may have resulted from adrenal atrophy (Stoner and Whiteley 1954). To prevent such deaths cortisone must be withdrawn gradually in patients treated for long periods, and really adequate doses must be given to cover the stress of operations or infections. Patients should carry a card with details of their treatment to warn doctors dealing with such emergencies. The weight and blood-pressure should be recorded regularly, the urine tested for sugar, and a chest radiograph taken every 6 months.

We conclude that prolonged treatment with steroids is justified and valuable in a small carefully selected group of patients who are severely disabled by chronic or frequently recurring asthma.

Summary

Fifty patients with severe chronic asthma were treated with cortisone, prednisone, or corticotrophin for a mean period of 2·7 years. The results were good in thirty-nine (78%). Apart from two cases of depression, side-effects were slight.

In a double-blind trial with eleven patients, nine relapsed during the control period, and one during the cortisone period. The probability that this was due to chance is 1 in 1000.

We are very grateful to Dr. Richard Doll for the design of the double-blind trial, and for assistance in the interpretation of its results; and to Dr. Horace Joules for help and advice. The control tablets were kindly supplied by Dr. H. M. Walker and Mr. J. C. H. Hanson of Glaxo Laboratories, Ltd., and we appreciate the cooperation of Miss K. Knight in dispensing them.

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SKIN CHANGES IN HYPOCALCÆMIA

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THE association of hair and nail anomalies with hypocalcæmia is well known, and the occurrence of cataracts also well recorded (Albright and Reifenstein 1948).

Simpson (1954) has classified the dermatological manifestations of hypocalcæmia due to hypoparathyroidism and steatorrhœa as follows:

(1) Abnormalities of nail and hair growth with latent or manifest tetany of acute onset.

(2) Skin, nail, and hair changes after prolonged hypocalcæmia.

(3) Secondary infection of skin and nail, often with monilia.

While the above trophic ectodermal lesions of hypoparathyroidism have been well recorded, only one reported case of exfoliative dermatitis in this disease could be found (Lachmann 1941) until the recent addition of one further case by Harell-Steinberg et al. (1957). This second case had generalised exfoliative dermatitis with sparse hair, leucocytosis, eosinophilia, and low serum-proteins with reversal of the albumin-globulin ratio. The skin improved with the administration of irradiated ergosterol. These two cases are extremely important since the serum-calcium level is not studied routinely in eczematous patients.

In the present paper we describe four further cases of hypocalcæmia. These differed in ætiology since one patient had permanent hypoparathyroidism following the removal of a non-toxic thyroid adenoma, one had severe but temporary hypoparathyroidism following the removal of a large parathyroid tumour, and two had steatorrhœa—idiopathic in one and probably cœliac in the other. These cases, and two further cases to be briefly mentioned, exhibited a dermatosis which could be related in onset and severity to the level of the serum (or plasma) calcium.

Methods

Plasma (or serum) calcium was determined by the standard macro method using oxalate precipitation and titration with permanganate.

Throughout this paper we use the term vitamin D to mean either vitamin D_2 (calciferol or ergocalciferol), vitamin D_3 (natural vitamin D or cholecalciferol), or dihydrotachysterol (D.H.T.). By 'AT10' we mean the proprietary form of irradiated ergosterol of which 1 ml. is stated to be equivalent to 1·25 mg. of pure D.H.T. Where we have used pure vitamin-D preparations the compound has been made up in our own pharmacy in peroxide-free arachis oil with antioxidant and given out in gelatin capsules of various sizes. Frequent assays have confirmed the stability of our preparations. We have preferred throughout to cite vitamin-D dosages on a mg. basis since in the treatment of hypocalcæmia dosages of all preparations thus expressed are closely comparable. 1 mg. of vitamin D_2 and of D_3—40,000 I.U. D.H.T. and AT10 have little antirachitic activity in the rat assay method so cannot be measured in international units.

Case-records

Case 1.—A married woman, aged 63, was admitted to University College Hospital on June 4, 1951, having been referred to us by Dr. D. Ferriman for further investigations as a possible case of hyperparathyroidism. She gave a typical history of increasing pain and muscular weakness, and investigations showed high calcium, low phosphorus, high phosphatase, and X-rays pathognomonic of osteitis fibrosa generalisata. A parathyroid tumour was found and removed on July 5, 1951, by Mr. W. R. Merrington, and she recovered well from the immediate effects of the operation. A week later, however, she developed acute anxiety (without any of the other signs of tetany) which was found to be due to hypocalcæmia, her plasma-calcium being then 5·6 mg. per 100 ml. These attacks were relieved by intermittent intravenous injections of calcium gluconate; but the calcium remained low in spite of this, although her bone pains and other signs were improving. On July 23, 1951, she developed a generalised rash with severe itching and swelling, especially of her face.

On examination she had generalised eczema particularly severe on the face, eyelids, trunk, and lower limbs. There was swelling of the face with erythema, scaling, and vesiculation together with excoriations on the arms and thighs. There was erythema with scaling of the scalp and sparseness of hair.

A drug eruption was thought to be the likely diagnosis, but the only medicament which was being used was calcium gluconate by intravenous injection. Intradermal skin tests with calcium gluconate were negative. The skin improved a week later and then in another fortnight became much worse with generalised œdema, especially of her face, so that she could not open her eyes. This rash was at first attributed to the intravenous calcium. It continued, however, when the injections were stopped for a short period and it did not heal finally for about two months. In retrospect the first temporary improvement (while large intravenous doses of calcium gluconate were being given) and her final spontaneous recovery coincided with rises of plasma-calcium to about 7 and to 8 mg. per 100 ml. respectively (see fig. 1). She was followed up for several years. Her serum-calcium remained normal; she had no further rash. We now have reason to believe that this patient also had occult idiopathic steatorrhœa as in the patient described by Davies, Dent, and Willcox (1956). Unfortunately the opportunity to confirm this diagnosis on a further admission to hospital has not yet arisen.

Case 2.—A married woman, now aged 68, was referred to the psychiatric clinic of University College Hospital by her private doctor on account of severe psychological changes. Dr. E. Roderic-Evans, who saw her there, thought that these might have been precipitated by disturbed metabolism and referred her therefore to one of us.

When seen here (Feb. 27, 1952) she was found to have pronounced symptoms and signs of tetany, a rash on her hands, and hopelessness, anxiety, depression, and fear of being alone.

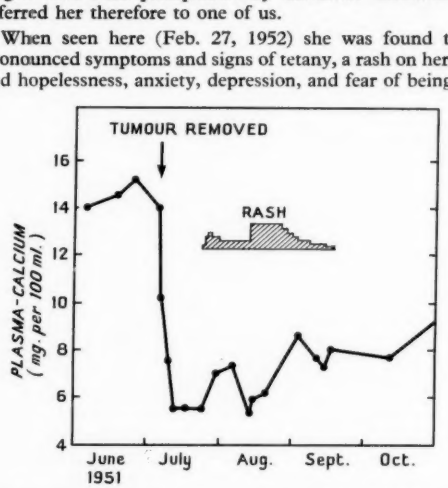

Fig. 1—Case 1: relation between plasma-calcium and intensity of eruption.

The rise in calcium during July 30 to Aug. 6, 1951, and on Sept. 3, 1951, coincided with heavy intravenous calcium-gluconate therapy. The final rise in calcium was probably spontaneous.

Fig. 2—Case 2: eczematous papulo-vesicles on the right arm with redness and scaling.

This eruption occurred on the limbs, face, and neck, whenever her serum-calcium level fell below 9 mg. per 100 ml.

These mental symptoms had recently been so bad that she had begun to consider taking her life.

All these troubles followed removal elsewhere of her thyroid gland in September, 1950, on account of a lump at first thought to be malignant. After the operation she was told that it had not been confirmed as malignant and that four glands behind the thyroid had also been removed. From then on she has been given thyroid medication. On account of the tetany she was also given at first AT10, but as this did not appear to help, injections of 'Parathormone' were begun. This relieved her symptoms and she left hospital well in November, 1950, still on parathormone. In January, 1951, she began to have attacks of vomiting, constipation, and weakness, diagnosed at first as "gastric flu". This continued till March, when this was shown to be associated with a serum-calcium of 18 mg. per 100 ml. and a blood-urea of 116 mg. per 100 ml. The parathormone was then stopped, and she got better and remained well for about four months. All the original symptoms returned, however, in October, 1951. She was then intermittently treated with AT10 and calciferol without much improvement. On Feb. 2, 1952, parathormone was again given. It relieved her symptoms for a week, after which it seemed to become ineffective, and she broke down mentally and was soon referred to the psychiatric department at University College Hospital, and thence to us.

She then reported that she had a rash between her fingers. This had come and gone with each previous worsening and improvement of her signs of tetany, and when severe had spread over her whole hands and forearms. On examination, she had gross tetany and was very disturbed mentally, feeling depressed and complaining about everything. No other physical signs of disease were discovered. Plasma calcium 5·9, phosphorus 6·6, mg. per 100 ml. Very thorough investigations were then undertaken in the metabolic ward of her response to parathormone and to oral AT10 and calciferol.

We found that she was difficult to control with either form of vitamin D, but we eventually worked out a suitable dosage and later changed her drug satisfactorily to pure D.H.T. We also confirmed the association between the rash (fig. 2) and the hypocalcæmia (fig. 3). From then until the time of writing (June, 1958) she has been regularly followed as an outpatient. She has shown herself to be unusually sensitive to variations in her plasma-calcium. Several times during this period she has developed early signs of tetany when her plasma-calcium has fallen slightly (below 9 mg. per 100 ml.), and at other times she has noted signs of milk intoxication when it has risen to only slightly abnormal levels (above 11 mg. per 100 ml.). Because of the difficulties in maintaining her plasma-calcium between the narrow limits, we had several opportunities to observe the effects of these changing levels. These effects were twofold: when the calcium was either high or low she became exceedingly depressed and mentally unstable; when it was low she also developed a rash, which always got better when the calcium was raised to normal or above normal. During this follow-up there were four further occasions (only two are shown in fig. 3) on which she had the rash in association with a plasma-calcium of less than 9 mg. per 100 ml. She has never had the rash when the plasma-calcium has been above 9 mg. per 100 ml. When present for only a short time the hypocalcæmia was associated with only minor itching and eczema between the fingers. On two occasions (fig. 3) it was more severe and of longer duration and comprised more generalised eczema affecting her lower limbs, face, and neck.

The rash occurring during October and November, 1952, was of particular interest. On this occasion we did not attribute the rash to the slight lowering of her plasma-calcium, for it appeared around her neck and seemed to be related to the dyed fur collar that she was wearing. When she stopped wearing the collar, the rash improved a little. She had a multicoloured jumper made of wool, which later appeared to produce an eruption on the neck, shoulders, arms, and wrists. At this time she was seen in the dermatological department, when patch tests with wool fibres from the incriminated jumper were performed. These patch tests were positive. During this period other garments were suspected of irritating the skin. The rash rapidly improved, however, when her plasma-calcium was raised to normal, so we presumed that the slightly low plasma-calcium (as later in 1956) was the main precipitating cause of this rash. Later, when the plasma-calcium level was restored to normal, the suspected garments could be worn again without causing irritation. Of especial note in this case was the fact that her plasma-calcium has been raised to normal on three occasions with parathormone, once perhaps as the result of a parathyroid graft and on all the other occasions with a form of vitamin D. The rash improved equally well whichever treatment was given.

Case 3.—A married woman, aged 61, was complaining of an eruption on her hands and arms which had been present on and off for the past eighteen years, though she remembered having occasional skin trouble for the past forty years.

When first seen by Dr. P. J. Hare in February, 1957, she had a rash on the hands and forearms which he thought was a contact dermatitis, though there were no apparent contact factors.

In July, 1957, she was admitted to St. Pancras Hospital under the care of Dr. J. F. Stokes. She was then in cardiac failure, with attacks of paroxysmal supraventricular tachycardia. She was noted to be of short stature and was found to have biochemical and X-ray evidence of osteomalacia. We thought that she was probably an adult survivor of cœliac disease. At this time, her skin disease was quite severe. Trousseau's sign was positive. She had redness, scaling, and slight oozing affecting the whole of her body surface except

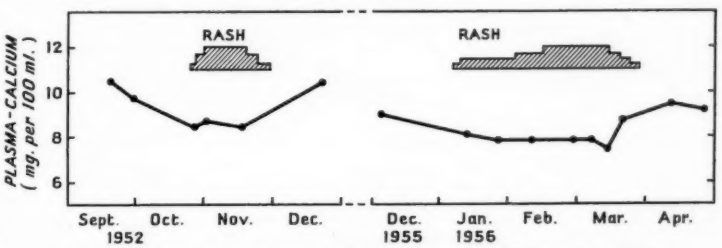

Fig. 3—Case 2: relation between plasma-calcium and intensity of eruption.

The fall in calcium in 1952 occurred immediately following insertion of a homologous parathyroid tumour into the patient's thigh, other treatment having been stopped. We believe it represents the slow and final death of the graft. After this the patient received AT10 for some while. The prolonged fall in calcium during early 1956 occurred during therapeutic trials of AT10 and pure D.H.T. in various doses, for which the patient had very kindly volunteered.

the face, which was relatively spared. The nails were thickened and the soles and palms were hyperkeratotic. The flexures were moistened by a serous discharge and were particularly severely affected. The scalp was very scaly, giving an overall impression of seborrhœic dermatitis in an erythrodermic phase. Her hair was thin and brittle.

Her hæmoglobin was 64% and the mean red-cell diameter was 7·5 μ. This macrocytic anæmia was thought to be an expression of her malabsorption syndrome, and her total fæcal fats were 63% (dry weight). Fat balance showed deficient absorption.

She was treated with digoxin and iron, and was given pure D.H.T. 1 mg. b.d. by mouth. A gluten-free diet was not considered practicable. Cardiac failure diminished, the plasma-calcium rose, and Trousseau's sign became negative. Between December, 1957, and February, 1958, she was maintained fairly well. The plasma-calcium remained low—approximately 8·0 mg. per 100 ml.—but her skin improved considerably. During January D.H.T. was omitted owing to a misunderstanding, and her plasma-calcium fell to 7·2 mg. per 100 ml. and the skin became much more red, scaly, and itchy. The dose of D.H.T. was raised temporarily to 15 mg. daily and then lowered to 5 mg. daily, and on this dose the plasma-calcium rose from 7·2 to 7·6 mg. per 100 ml. over the course of four weeks (see fig. 4).

She improved so much that she was allowed to go home for Easter in April, 1958. After three days at home during very cold weather, she returned having changed greatly. Her rectal temperature was 86°F and she was very sleepy. She died in coma on April 9, 1958.

Postmortem examination showed the presence of bronchopneumonia, and there were pinpoint yellow areas surrounded by hæmorrhage in both adrenal cortices. It was thought that this patient died of hypothermia.

Case 4.—A man, aged 63, first attended the dermatological outpatient department in 1953 complaining of a rash which he had had on his legs for the past three months. He admitted to some recent loss of weight and had suffered from indigestion. The rash was worst on the legs behind the knees and on the sacrum (fig. 5). The rash consisted of blue-red erythema with oozing and crusting in the groins, around the genitalia, and on the thighs, buttocks, and sacral area. In these areas there was dark bluish-brown pigmentation, with thick scaling and crusting in the folds. The eruption was foul-smelling and tacky, and more peripherally there were brown pigmented lichenified areas with bluish-red papules, ill defined, 3–4 mm. in diameter. The natal cleft was sore. The rest of the body was pigmented, pale fawnish-yellow. There was fœtor from the mouth; the corners of the mouth were crusted. *Candida albicans* was grown from the mouth and from the groins. The nails were grossly thickened, and the tongue was glazed and atrophic.

He was admitted to hospital but could not stay in for long and was discharged after a month somewhat improved. His rash slowly healed with pigmentation, but relapsed to its former state. Grenz rays and local applications helped him to some extent.

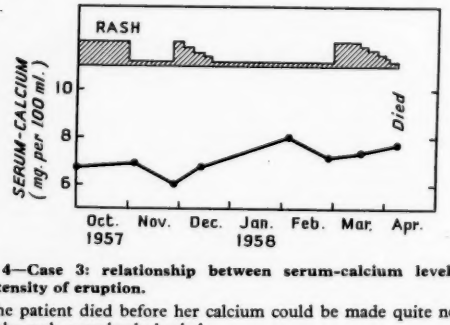

Fig. 4—Case 3: relationship between serum-calcium level and intensity of eruption.

The patient died before her calcium could be made quite normal and the rash completely healed.

He remained fairly well during 1954, though his skin was always rough and scaly, and in 1955 he was readmitted. He was found to have macrocytic anæmia, and was treated with local applications and vitamin B_{12}. He was discharged improved.

In 1957 he was once more admitted with generalised erythroderma, severe pigmentation, and macrocytic anæmia. He was prematurely bald and had clubbed fingers. Dr. J. Nelms (house-physician) suggested that the patient was suffering from steatorrhœa, and the fat-balance and X-ray pictures of barium meal and follow-through confirmed this view. He had had chronic bronchitis on and off for ten years, but soon after admission he had an attack of stridor, tingling in the hands, and muscle cramps. His serum-calcium level was found to be 5·0 mg. per 100 ml. and his phosphorus 1·0 mg. per 100 ml. Trousseau's and Chvostek's signs were positive.

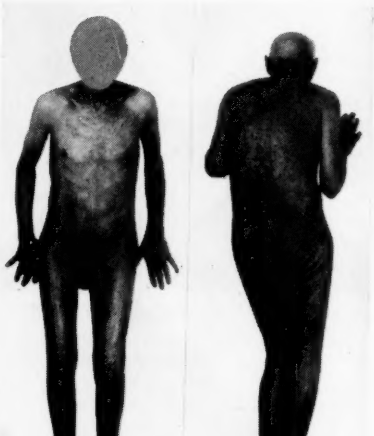

Fig. 5—Case 4: redness, scaling, and vesiculation mainly on the trunk and lower limbs.

There is pronounced pigmentation of the skin, especially intense in areas affected by the eczematous changes. Photograph taken before steatorrhœa was diagnosed, when the serum-calcium was probably in the region of 5 mg. per 100 ml.

He was then seen by one of us (C. E. D.) who agreed that the low serum calcium and phosphorus were due to steatorrhœa. Raising his serum-calcium by means of pure calciferol 5 mg. b.d. by mouth improved his chest condition and caused his cramps to disappear and his eczema to heal. He was also given 'Diodoquin' (di-iodohydroxyquinoline) orally at first, but it was not considered to have played a part in his improvement and was later stopped.

He was discharged well, and remained in fairly good health until his calciferol was stopped in May, 1957, when calciferol ('Sterogyl') 50,000 I.U. (1·25 mg.) b.d. by mouth was substituted to see if this helped more. He rapidly deteriorated; he became weak, and redness and scaling reappeared. His serum-calcium level fell to 5·3 mg. per 100 ml. Treatment by mouth with pure calciferol (5 mg. t.d.s.) was reintroduced. The serum-calcium level was restored to normal and the skin rapidly improved (fig. 6).

He continues to be treated with vitamin B_{12} and oral calciferol (5 mg. b.d.) and remains well.

The eczema which became generalised and produced an exfoliative dermatitis in this man was peculiar in that deep pigmentation occurred. Skin pigmentation is a common feature in steatorrhœa, and it is thought that it was the presence of steatorrhœa which determined the pigmentation in this patient. The pigmentation which he exhibited was, however, more bizarre and deeper than is usually associated with that condition.

Biopsy showed the histological features of eczema with deposits of melanin deep in the dermis as well as in and around the basal-cell layer. No evidence of abnormal deposition of iron pigments in the skin could be found.

Discussion

We have described here four patients in whom there appeared to be a constant association of a dermatosis with a lowering of their serum (or plasma) calcium levels, the condition always being reversible by raising the calcium to normal. We are not aware that this matter has been reported before in these terms, although it is perhaps not surprising in view of the known associations between hypocalcæmia and other skin lesions. These known associations, mentioned in the introduction of this paper, have occurred when the hypocalcæmia was due to hypoparathyroidism or steatorrhœa. In the cases we describe, these ætiologies are also concerned. That it is the lowered calcium level that is the main cause of the skin lesions seems quite clear, for not only are there several causes of hypocalcæmia, but it seems to be immaterial which particular means was used for raising the calcium to normal. For instance, among these have been the spontaneous return of the patient's parathyroid function, injections of crude parathyroid extract obtained from animals (parathormone), injections of calcium gluconate, and oral treatment with pure calciferol, pure D.H.T., or irradiated ergosterol (AT10). In most instances no other treatment than that mentioned above was given at the time. Local treatment to the skin consisted in bland applications throughout.

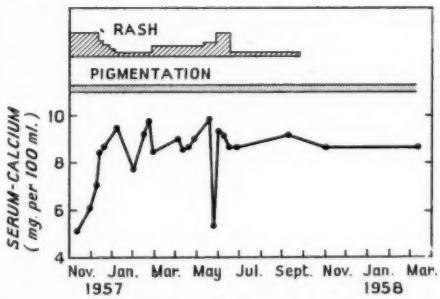

Fig. 6—Case 4: relation between serum-calcium level and intensity of eruption.

The acute fall in serum-calcium during May, 1957, coincided with a change of treatment to sterogyl, which in the dosage used proved to be ineffective. The serum-calcium level rose again when pure calciferol was reintroduced.

Clearly these skin lesions are an uncommon complication of hypocalcæmia. Apart from these four patients we have so far observed only two further cases in which itching and skin disease developed together with temporary hypocalcæmia. We think these are probably true examples of the phenomenon, but the investigations are inadequate for publication here. There must also be a strong and constant individual factor involved, for the patients mentioned here have always had the rash when we know, or can presume, that their calcium was low. It is clearly important to consider this possible cause of skin disease, especially bearing in mind that the treatment with vitamin D is very adequate and that there seems in such cases to be no alternative treatment.

We wish to stress strongly that classical signs of tetany do not need to be present with marked hypocalcæmia. This is a well-known clinical observation, although published reports do not stress it. Of our cases, case 1 showed this feature conspicuously, for she was repeatedly observed over a period of three months with very low calcium levels, but never manifested positive Trousseau or Chvostek signs, spontaneous cramps, or carpopedal spasms. It was fortunate that in her particular case we were expecting her calcium to fall owing to her having had a large parathyroid tumour removed and having with it very severe bone changes. In two of our other cases it is painfully apparent that we were much slower to make this diagnosis. We can only suggest that if an adult patient with skin disease and no signs of tetany has a scar on the neck or is less than 5 ft. tall, the plasma-calcium should certainly be determined—perhaps sometimes in even less obvious circumstances.

Impetigo herpetiformis was first described by Hebra (1872) and is a pustular dermatosis associated with fever and severe prostration. Four of his five cases died. Some hundred cases are now recorded, and these were reviewed by Hvidberg (1957). The disease is more common in women, though cases are recorded in men. Women very often acquire the disease, or recurrence of it, during or immediately after pregnancy. A striking proportion of women have a history of thyroidectomy. Beek (1951) records typical hypoparathyroidism in twenty-four out of fifty-seven cases. He concludes that some cases are due to endocrine imbalance, while some are caused by an infection. While this severe pustular disease bears no clinical resemblance whatever to the cases of "hypocalcæmic dermatitis" which we have described, the relationship to parathyroid function seems to be more than a coincidence. One of Hvidberg's cases, a woman with typical impetigo herpetiformis in pregnancy, proceeded to have attacks of generalised erythroderma twelve years later.

Many workers have considered the dermatological significance of calcium metabolism. The subject was reviewed by Goldsmith and Hellier (1954), and Wiener (1955) mentions the anti-inflammatory action of calcium therapy in mustard-oil conjunctivitis experimentally induced in rabbits. Calcium-gluconate injections have been used in the treatment of urticaria, pruritus, and eczema, with varying results. The value of this mode of treatment may be explained on the basis of the work of Chambers and Zweifach (1947). These workers believe that calcium ions are required to restore the damaged cement substance which serves in the densification of vessel walls.

Calcium metabolism has been studied in many other dermatological conditions. The fact that calciferol itself, or perhaps the mild hypercalcæmia resulting from its administration, can profoundly affect the skin reactivity to disease processes is quite obvious from the common clinical experience of the remarkably beneficial effects of calciferol in lupus vulgaris, though this is rather a special case. Furthermore our case 2 was shown to be sensitive to dyed wool fibres only while she was hypocalcæmic. This situation may clearly be of practical importance in skin testing to external irritants. In this paper we have not, however, attempted to explain the skin changes in cases of hypocalcæmia in terms of disordered skin physiology, since we have nothing to add to this difficult matter.

Summary

In patients with diseases of three different ætiologies, severe skin changes were closely associated with temporary hypocalcæmia.

In each case dramatic improvement occurred, often repeatedly, when the plasma (or serum) calcium became normal or was restored to normal with vitamin D, parathyroid hormone, or calcium-gluconate injections.

These facts are considered to be highly suggestive of a close association between "skin health" and plasma-calcium levels in certain patients.

Since the presence of hypocalcæmia may not be clinically obvious from the presence either of overt tetany or of a known cause of tetany, this possibility should be borne in mind, especially as treatment is so satisfactory.

We wish to thank Dr. J. F. Stokes for permission to publish case 3, and Dr. P. J. Hare for case 4. Mr. A. Bligh kindly took the clinical photographs and Mr. V. K. Asta drew the diagrams.

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OVERWEIGHT IN PREGNANCY

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THAT overweight in pregnancy increases the risk to the fœtus has long been known (Smith 1916).

Matthews and der Brucke (1938) studied 200 pregnant women whose weight was over 200 lb. 75% of them had some complication of labour. They showed a pronounced increase in the incidence of pre-eclamptic toxæmia, malpositions, long labour, maternal distress, and operative delivery. These findings were confirmed by Odell and Menger (1945). Tompkins et al. (1955) found that patients 20% or more overweight or underweight were especially likely to develop pre-eclamptic toxæmia. Williams (1957) found that in cases of pre-eclamptic toxæmia the patients' initial weight as well as weekly gain during pregnancy were on average higher than normal.

Hamlin (1952, 1953) found that one of the most important factors in the prevention of eclampsia and pre-eclamptic toxæmia was control of diet and weight gain in pregnancy. He reported that by this means he had reduced the incidence of eclampsia from 1 in 500 to 1 in 7000.

Another danger of excessive weight gain in pregnancy is that the patient may remain permanently obese (Gurney 1936, Greene 1939, Sheldon 1949, Richardson 1952). In a personal series of 300 obese parous women attending a medical outpatient department, 226 (72%) stated that their obesity dated from pregnancy.

Only 45 of these had shown any previous tendency to obesity. In all but 30 the obesity had increased with every pregnancy. Moreover, there seems little doubt that their maternal obesity seriously impaired their health. 50 of them, seen consecutively, were matched for age and sex with 50 medical outpatients who were not obese. It was found that in the previous five years the obese group had had three times as many hospital appointments as the non-obese group, chiefly in the departments of gynæcology, surgery, physical medicine, and casualty. They had also been admitted to hospital more frequently, chiefly for minor gynæcological procedures. There is growing evidence that successful treatment of their obesity has improved the general health of these women and considerably reduced the frequency of their attendances at hospital.

Hamlin (1952, 1953) believes that primiparæ should not gain more than 8 lb. (3·6 kg.) between the 20th and 30th weeks of pregnancy. Hughes (1951) stated that a gain of more than 1 lb. per week after the fifth month of pregnancy pointed to the need for close observation of the patient. A woman whose initial weight for height is more than 25% above any " standard " table is, by general agreement, overweight, and a weight gain of more than 28 lb. during pregnancy is generally regarded as excessive. All the patients studied here were outside these standards, many of them considerably.

Sheldon (1949, 1953) and Richardson (1952) agreed that excessive increase of weight during pregnancy was due to increased appetite and stressed the possible importance of psychogenic factors. A patient in the present series stated that she always knew when she was pregnant, even before the first missed period, because she felt unusually hungry. Many patients who gain excessive weight in pregnancy feel hungry all the time. 100 consecutive patients in the present series were asked about this and 52 admitted to it. Others found that the frequent ingestion of carbohydrate was the best way to control nausea. A woman who normally controls her appetite for the sake of her figure may regard her inevitable change of shape during pregnancy as a justification for " letting herself go "; she may believe that she must " eat for two ", or fear that, by depriving herself, she is depriving the child. Lastly, many women who give up work during pregnancy are bored while waiting for their babies; they find themselves at home all day, surrounded by food, and eating helps to pass the time.

Material

This is an account of the management during pregnancy of 25 multiparous patients each of whom had, during one or more previous pregnancies, gained 42 lb. or more, and of 10 primiparous patients who, in the first five months of pregnancy, gained a minimum of 20 lb. 15 of the patients in the multiparous group were being treated by me for obesity when they became pregnant; and, of these, 7 had reached normal weight. The remaining 10 multiparæ were referred from the antenatal clinic because of their histories of excessive weight gain; and, of these, 7 were obese. All the primiparous patients were referred from the antenatal clinic on account of excessive weight gain.

Methods

These patients were all treated in the obesity clinic, which is part of the medical outpatient department of St. James' Hospital. As far as possible they were seen immediately after their visits to the antenatal clinic.

At the first visit a medical history was taken and the patient was fully examined. In addition, information was sought concerning appetite and food habits and the kind of life the patient led, so that her eating habits could be adapted to it. Special note was taken of food preferences and of cravings for special articles of food. A history of obesity in the patient's family was also recorded.

Advice was then given about the diet. In all cases a low-carbohydrate diet was recommended. Typical advice was: " Eat not more than two slices of bread per day and nothing else whatever containing flour, sugar, or potato. Eat as much as you like of meat, fish, eggs, vegetables (other than potato), salad and fresh fruit ". Patients who were eating large quantities of foods such as rice or nuts were advised to reduce their intake of these. It was often necessary to enlarge on details—for example, to emphasise that all biscuits and bread contain flour, and that an article of food may not be eaten just because it is advertised as " non-fattening " or " slimming ".

Drugs were only used when it was considered that the patient's weight could not be controlled without them. 4 of the multiparous patients had been on dexamphetamine sulphate before they became pregnant, and these were kept on the drug throughout. 2 other multiparæ and 1 primipara were started on dexamphetamine sulphate during pregnancy. There is no

evidence that this drug is contraindicated in pregnancy, and no ill effects were observed.

These patients were all seen by me at intervals of one to four weeks. The interval depended on the degree of difficulty experienced by the patient in controlling her food intake, and on her weight change between visits.

Results

During the pregnancies the 25 multiparæ gained an average of 18 lb. (standard deviation 10 lb.) compared with an average of 59 lb. (standard deviation 16 lb.) in previous pregnancies when their weight had been unsupervised and 49 lb. (standard deviation 14 lb.) in pregnancies where their weight had been supervised in the antenatal clinic. Only 3 of them gained 28 lb. or more, and 2 of these had already gained 24 and 26 lb. when referred to the obesity clinic at 20 and 19 weeks respectively.

The 3rd had had uncontrollable craving for chocolate since childhood, and this increased during pregnancy. She gained 36 lb. during this, her third, pregnancy, which was the largest gain in the group. During her second pregnancy she had gained 49 lb. despite attempts in the antenatal clinic to control her weight. During her first pregnancy she had received no instruction regarding her weight and had gained 63 lb.

Among the 10 primiparæ and 10 multiparæ referred from the antenatal clinic on account of excessive weight gain, the average weekly gain fell from 1·8 lb. (standard deviation 0·4 lb.) to 0·6 lb. (standard deviation 0·2 lb.) although they attended the obesity clinic in the second half of pregnancy, when weight gain is normally greatest. None of these patients gained more than 14 lb. after the 20th week of pregnancy, or more than 9 lb. during the 20–30 week period. The 10 multiparous patients had, during their previous pregnancies, gained excessive weight throughout.

All the 35 pregnancies in which the weight gain was controlled in the obesity clinic ended in the normal delivery of a healthy infant. In the previous 43 pregnancies of these women in which the weight gain had not been successfully controlled, there had been 5 stillbirths, 6 forceps deliveries, 3 cæsarean sections, and 8 cases of pre-eclamptic toxæmia necessitating admission to hospital.

Discussion and Conclusion

Experience in treating obesity has shown that advice, however sound, is seldom sufficient for satisfactory weight loss when it is given only once. The patient must be seen at short intervals to reinforce and repeat the advice and to encourage, praise, or admonish. In difficult cases it is often necessary to discuss in detail the patient's eating habits, to vary the diet in accordance with her life circumstances, to suggest recipes and methods of food preparation, and to encourage the patient to try new articles of food: repeated encouragement and advice are especially necessary in such cases because long-standing habits are hard to change, and the attempt often causes the patient much anxiety.

By these methods many obese patients, hitherto regarded as "untreatable", can be helped to regain normal weight. The same principles have been applied successfully to patients with excessive weight gain in pregnancy, not controlled by advice in the antenatal clinic. Since pregnancy is a common starting-point of obesity in later life, the control of excessive weight gain in pregnancy is important, not only for the outcome of the pregnancy, but also for the future health of the patient.

This work was done during the tenure of a Nichols research fellowship of the Royal Society of Medicine.

(*References at foot of next column*)

TOTAL EXCHANGEABLE POTASSIUM IN INFANTILE MALNUTRITION

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ONE of the characteristics of severe protein malnutrition in infants is a profound electrolyte disturbance (Gomez et al. 1957). Balance experiments (Hansen and Brock 1954) have provided indirect evidence of a depletion of potassium and an accumulation of sodium in the body. These changes are reflected in muscle, as shown by the analysis of biopsy specimens (Frenk et al. 1957, Waterlow and Mendes 1957). Further evidence of potassium depletion has now been obtained by measurement of total exchangeable potassium (Ke).

Since the original observations of Corsa and his associates (1950), many studies on exchangeable potassium have been made in adults, in both health and disease (O'Meara et al. 1957, Edelman et al. 1958, Flear et al. 1958). Studies have also been reported in normal neonates (Christian and Talso 1959), normal infants and children (Corsa et al. 1956), and in children with the nephrotic syndrome (Gribetz et al. 1954). We have, however, been unable to find any record of such measurements in malnourished children.

Method

^{42}K,† as a sterile solution of potassium chloride, was given by intramuscular injection in a dose of 1 μC per kg. body-weight.

The amount injected must be accurately known. This was achieved by weighing the bottle containing the solution before and after filling the syringe. The syringe was washed out after the injection, and the radioactivity measured in the washings.

Exchangeable potassium (Ke) was calculated from measurements on the urine.

Blood was not used, because an unjustifiably high dose of isotope would be needed to obtain a measurable level of radioactivity. Moreover, in these severely ill children the number and size of blood samples removed should be kept to a minimum. Wherever possible three separate samples of urine were collected at intervals from 22 to 31 hours after the injection. In all the later measurements the urine was concentrated about five times by evaporation in order to increase the accuracy of the counting. Radioactivity was measured with a well-type scintillation counter; urinary potassium was measured with the flame photometer.

Exchangeable potassium is given by the formula:

$$Ke\ (mEq.) = [(\text{counts injected}) - (\text{counts lost between injection and measurement})] \times \frac{^{39}K \text{ concentration in urine (mEq. per litre)}}{^{42}K \text{ concentration in urine (counts per litre)}}$$

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† Obtained from Atomic Energy Research Establishment, Harwell, Berkshire.

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TABLE I—PRELIMINARY STUDY OF EXCHANGEABLE POTASSIUM IN 12 CASES OF INFANTILE MALNUTRITION

Patient no.	Age (months)	Weight (Kg.)	Total Ke, mEq.	Ke per Kg. body-weight, mEq.
Early cases:				
1	12	4·90	145	29·6
2	6	5·35	159	29·7
3	5	3·18	91	28·6
4	5	3·35	152	45·4
5	10	5·95	170	28·6
6	10	4·22	72	17·1
7	20	7·40	209	28·3
8	9	5·30	86	16·2
Recovered cases:				
9	18	6·84	264	38·6
10	18	6·10	287	57·0
11	7	6·35	203	31·8
12	18	4·10	157	38·3

In most cases a complete collection of urine was made from the time of injection to the time of measurement. The urinary loss of isotope was then measured directly and averaged 4·7% of the injected dose in the first 22 hours. When for any reason urine collections were incomplete the urinary loss of isotope was estimated as 5% of the dose.

No allowance has been made for fæcal loss.

In the adult this is normally insignificant compared with the amount lost in the urine (Corsa et al. 1950). However, in infants with diarrhœa and coexistent potassium depletion the fæcal loss of potassium may exceed the urinary loss. The effect of neglecting fæcal loss will be to increase the apparent value for Ke. In adults it has been recommended (Corsa et al. 1950) that oral potassium intake should be restricted during the period of measurement. We did not think it justifiable to do this in our cases.

In the present series, equilibration of injected ^{42}K, as judged by a constant specific activity in the urine, appeared to be virtually complete by 22 hours. In adults 95% equilibration occurs between 18 and 40 hours after injection, even in the presence of œdema (Corsa et al. 1950, Blainey et al. 1954, O'Meara et al. 1957).

Material

The cases studied presented the clinical characteristic of severe malnutrition that have been described in previous reports from Jamaica (Waterlow 1948, Jelliffe et al. 1954).

Results

A preliminary study was made in twelve cases (table I). The urinary loss was not measured directly, but was assumed to be 5% of the dose. The mean Ke in eight malnourished babies soon after admission to hospital was 27·9±3·0 mEq. per kg. body-weight, and in four recovered cases 38·9±2·8 ‡ mEq.

The results in a second series of twenty-two cases are summarised in table II. The mean Ke in six babies who had been in hospital for less than a week was 31·6±3·2 mEq. per kg. In sixteen children who had been in hospital for more than a week the mean Ke was 41·4±1·3 mEq.

‡ Standard error of the mean.

The results expressed in this way indicate that on the average the malnourished babies had lost about 25% of their exchangeable potassium.

In our cases the serum-potassium level gives no indication of the presence of extent of body-potassium depletion. This agrees with previous observations, such as those of Moore et al. (1954) on adults.

Muscle, on the other hand, reflects more closely the changes in Ke. In thirteen cases muscle biopsies were done at the time of measurement of exchangeable potassium. The muscle potassium content was measured by the method previously described (Waterlow and Mendes 1957), and related to D.N.A. (desoxyribonucleic acid) phosphorus, as the most constant cellular constituent.

Fig. 1 shows that there was a good deal of variation; but even in this small number of cases a significant correlation was obtained between Ke and the potassium content of muscle. Red-cell potassium seems not to vary in the same way as muscle potassium (V. G. Wills, unpublished data). From the practical standpoint this is unfortunate, since it would be so much easier to measure.

TABLE II—EXCHANGEABLE POTASSIUM IN 22 CASES OF INFANTILE MALNUTRITION

Time in hospital	No. of cases	Mean Ke per Kg. body-weight (mEq.)
Less than a week	6	31·6±3·2
More than a week ..	16	41·4±1·3

There is evidence that one effect of cellular potassium depletion is an inability on the part of the kidney to concentrate hydrogen ion after an acidifying dose of ammonium chloride (Clarke et al. 1955, Smith 1959). This test was done in twenty-one cases immediately after the measurement of exchangeable potassium. Fig. 2 shows a close correlation between the extent of potassium depletion and inability to acidify the urine.

Discussion

Our observations confirm the original finding of Hansen and Brock (1954) that infants with protein malnutrition are severely depleted of potassium. They suggest, moreover, that this depletion affects cell function in at least one organ, the kidney. On the other hand the quantitative interpretation of the results is not easy, since no standard of reference is entirely appropriate. In well-nourished children with gastroenteritis there is a loss of potassium in excess of the loss of other tissue components (Darrow 1946). But in these malnourished infants it may be argued that the reduction in Ke merely reflects a reduction in tissue mass, and not a *specific* depletion of potassium. To some extent this is true: measurements of body water (Smith, to be published) have shown that even in the absence of œdema the body of the malnourished baby contains an increased proportion of water, and hence a decreased proportion of solids. In the present

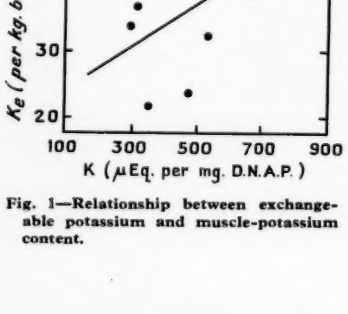

Fig. 1—Relationship between exchangeable potassium and muscle-potassium content.

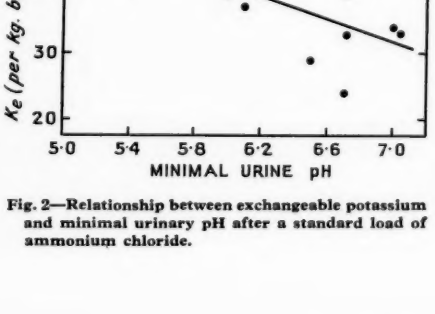

Fig. 2—Relationship between exchangeable potassium and minimal urinary pH after a standard load of ammonium chloride.

study we have not measured Ke and total body water at the same time in the same case. Therefore we are not able to state with certainty whether the depletion of potassium is greater or less than that of the body solids as a whole. In one tissue, muscle, there is evidence of a specific or extra loss of potassium, since the ratio of potassium to non-collagen nitrogen is significantly lower than in normal muscle, even after 7–10 days treatment (Waterlow and Mendes 1957). This fits in with Hansen and Brock's (1954) finding that during recovery more potassium was retained than nitrogen (in comparison with the ratio of these two elements in normal tissues); but it cannot be assumed without further investigation that a specific loss of potassium occurs from organs other than muscle.

From the practical point of view, these measurements suggest that the malnourished infant may have lost at least a quarter of its exchangeable potassium; thus an infant of 6 kg. might have a deficit of some 60 mEq. In this unit we normally give a potassium supplement of about 20 mEq. per day (as potassium acetate), in addition to the 15 mEq. or so supplied by the diet. Even when muscle analysis indicates that the body is depleted of potassium, balance measurements show that retention of ingested potassium is by no means completely efficient. Supplementary potassium must therefore be continued for a considerable period—perhaps for 10 days or more. Restoration of a normal serum-potassium level must not lead one to assume that the body stores are repleted.

Summary

In infants with severe chronic malnutrition the total exchangeable potassium (Ke) was measured by the isotope dilution method. Ke per unit body-weight was found to be reduced by 25–30%. After recovery normal levels were found.

The reduction in Ke was accompanied by a loss of potassium from muscle, and by inability to produce an acid urine in response to a test dose of ammonium chloride.

The serum-potassium level is no guide to the extent of depletion of body-potassium.

In treatment it is necessary to continue potassium supplements for at least 10 days, since even in the presence of depletion potassium is incompletely retained.

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New Inventions

A SPIROMETER FOR MEASURING THE FORCED EXPIRATORY VOLUME WITH A SIMPLE CALIBRATING DEVICE

THE forced expiratory volume (F.E.V.), or amount of air a subject can exhale forcibly in a short time (usually 0·75 sec. or 1 sec.) after a full inspiration, is now widely used as a measure of ventilatory capacity (for terminology see Gandevia and Hugh-Jones.[1]) It can be measured either by a recording spirometer with fast recording kymograph [2] or with a simple spirometer, the rotation of whose wheel shows the volume expired. The volume over a fixed time period is recorded by a pointer lightly held at the centre of this wheel and restrained from moving with it during the selected time by a solenoid actuated by an electronic timer.[3]

The latter type of apparatus, of which an improved form is described here, has the advantage of providing a reading without the necessity of analysing a paper record, and is thus well suited both for routine use in the clinic where an immediate answer is needed and for field surveys where large numbers must be rapidly examined. Up to the present a major disadvantage of this type of instrument has been that it is possible for errors in the electronic timer and relay to go undetected. The testing device described here overcomes this difficulty.

1. Gandevia, B., Hugh-Jones, P. *Thorax*, 1957, **12**, 290.
2. Kennedy, M. C. S. *ibid.* 1953, **8**, 73.
3. Gaensler, E. A. *Science*, 1951, **114**, 444.

Spirometer

The spirometer (fig. 1) has a 7-litre bell and a breathing tube of $1^3/_8$ in. diameter set at an angle of 45° to the canister so that compensation can be made for tables of different heights. This tube has a small inspiratory valve in the lower side to prevent

Fig. 1—The apparatus with calibrating device.

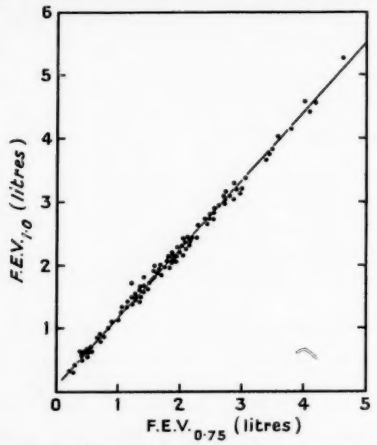

Fig. 2—The relationship between F.E.V.$_{0\cdot75}$(x) and F.E.V.$_{1\cdot0}$(y) in 100 subjects. The straight line is the linear regression $y=1\cdot08x+0\cdot09$.

aspiration of water by the subject. The black bakelite wheel on the spirometer head has a double white engraved scale, the outer one in litres and 0·05 litre, and the inner one, for recording the indirect M.B.C., in litres per minute. The latter scale (the E.F.R.$_{40}$ of Kennedy) is the F.E.V.$_{0\cdot75}$ multiplied by 40, and should therefore only be used when the timer is set for 0·75 sec. Both scales are corrected to B.T.P.S., assuming a water temperature of 20°C. Their accuracy at this temperature is within ±1·5%. A change of ±5°C will cause an error of less than ±2% in the readings, and it is therefore usually unnecessary to correct them further.

There are two pointers, the fixed one indicating the vital capacity and the movable one the F.E.V. The back end of the movable pointer engages a catch operated by the solenoid which is only energised during the time period set on the electronic timer. The timing cycle, which is adjustable, is initiated through a microswitch on the head immediately 100 ml. of air has entered the spirometer. This 100 ml. volume delay is incorporated to reduce errors in readings due to the subject hesitating at the start of expiration. It makes no appreciable difference in normal breaths as the pointer is arranged not to pass the zero until this volume has been expired.

The timer, manufactured by Venner Electronics Ltd., is mains operated from an alternating current supply of 200–250 volts and 40–60 cycles per sec. It can be set to operate over any time periods from 0·5 to 3·0 seconds.

The Calibrating Device

This consists of a 1-in. length of 'Tufnol' rod bored to $^1/_2$ in. internal diameter and made to attach to the spirometer in place of the breathing tube, and a 500 g. weight which is hung on the hook at the bottom of the existing counter-weight. The tufnol tube is accurately machined, and damage to its bore will affect the calibration.

With the calibrating tube and extra weight in place the spirometer bell is gently depressed until the block on the spirometer wheel makes contact with its stop. It is then suddenly released and air is drawn through the orifice into the bell at a flow-rate which is constant for a given spirometer, tube, and weight; the machine will therefore record its own F.E.V., the values of which, corresponding to time intervals of 0·75 and 1·0 second, are supplied with each apparatus. The mean of three readings should agree with the appropriate stated value within ±0·05 litre and the individual readings should not deviate from each other by more than this amount, as the repetitive accuracy of the timer is ±2%. If the mean lies outside these limits the cause should be sought and if necessary the timer adjusted.

As the air-flow rate at the end of the first 0·75 or 1·0 second of a forced expiration is relatively very low compared with the earlier part, an error in the timer giving a change in the calibration within these limits has been found to affect the recorded F.E.V. less than ±0·6%.

Time Interval

The F.E.V. is commonly measured over either 0·75 or 1·0 second and in order to relate these values we studied 100 subjects using a special apparatus with two pointers operated by separate timers. The group comprised 20 members of the staff, 60 employees of a light industrial factory for men partially disabled by coalworkers' pneumoconiosis, and 20 inpatients mainly suffering from pneumoconiosis and chronic bronchitis.

Fig. 2 indicates that the relationship throughout the whole range of values can be adequately described for practical purposes by a straight line ($r = 0\cdot998$). However the tendency for the scatter to increase at the higher values of F.E.V. suggests that a logarithmic relationship would give a better indication of the range of accuracy of conversion that can be attained. Fig. 3 shows the least-squares regression fitted to the logarithms of the F.E.V. values, and 95% fiducial limits, for predicting the F.E.V.$_{1\cdot0}$(y) from the F.E.V.$_{0\cdot75}$(x).

Also shown is the simple linear regression

$$y=1\cdot08x+0\cdot09,$$

which it will be seen lies within the 95% limits and will lead to perfectly acceptable values at all points in the scale.

The same is true if the linear regression

$$x=0\cdot92y-0\cdot07$$

is used to predict the F.E.V.$_{0\cdot75}$ from the F.E.V.$_{1\cdot0}$.

Thus we may predict the F.E.V.$_{1\cdot0}$ from the F.E.V.$_{0\cdot75}$ simply

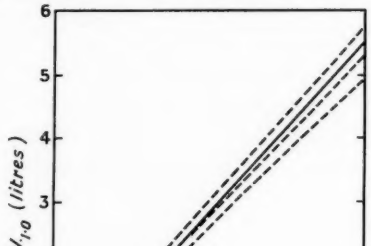

Fig. 3—The relationship between F.E.V.$_{0\cdot75}$(x) and F.E.V.$_{1\cdot0}$(y). Continuous line: Linear regression $y=1\cdot08x+0\cdot09$. Broken lines: Logarithmic regression $y=1\cdot191x^{0\cdot931}$ with 95% fiducial limits.

by taking 108% of the latter and adding 0·09 litre to it. Similarly the F.E.V.$_{0\cdot75}$ can be predicted from the F.E.V.$_{1\cdot0}$ by taking 92% of the F.E.V.$_{1\cdot0}$ and subtracting 0·07 litre.

Since this work was done Miller et al.[4] have published data on the relationship between the forced vital capacity and F.E.V.$_{0\cdot5}$, F.E.V.$_{0\cdot75}$, and F.E.V.$_{1\cdot0}$. From these it is possible to calculate approximately the relation between the F.E.V.$_{0\cdot75}$ and F.E.V.$_{1\cdot0}$ and this agrees well with our findings.

The F.E.V. Test

The spirometer bell is fully depressed and the movable pointer set to about 0·5 litre. (The exact figure is immaterial provided it is less than the F.E.V. measured.) The seated subject is asked to inspire maximally, then to place his lips firmly around the mouthpiece, and to blow as hard as possible. There is good evidence that the first and perhaps second attempts tend to be low compared with the subsequent ones, and it is therefore advisable to allow the subject two trial blows and then to average

4. Miller, W. F., Johnson, R. L., Jr., Wu, N. *J. appl. Physiol.* 1959, **14**, 157.

the following three consecutive ones provided they are technically satisfactory. If desired each breath can be followed through to maximal expiration to obtain the vital capacity although this adds considerably to the fatigue of the test. If the vital capacity is not measured, no more than half a minute's rest need usually be allowed between blows. A nose clip is unnecessary.

The apparatus and calibrating device were developed in the Research Unit's workshops by Mr. F. Hyett, to whom we are grateful for many suggestions. The instrument is now obtainable complete from D. Poulton & Son, 19, Tan-y-fron, Garden Suburb, Barry, Glamorgan. Our thanks are also due to Mr. P. D. Oldham for statistical advice and to Miss Pamela Edwards for technical help.

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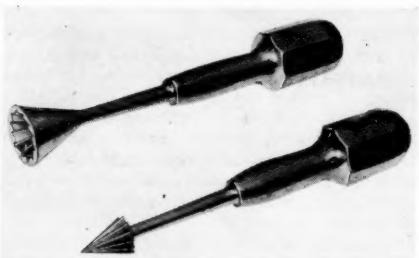
A REAMER AND BURR FOR ARTHRODESIS OF THE METATARSOPHALANGEAL JOINT

THESE instruments are designed to facilitate arthrodesis of the metatarsophalangeal joint of the hallux in cases of hallux valgus and hallux rigidus. After exposure of the joint the metatarsal head is shaped into a conical peg by means of the specially designed reamer. Preliminary shaping with an osteotome or bone-cutting forceps may be required when the



joint surfaces are hard and eburnated. The base of the proximal phalanx is then hollowed out with the large burr. The reamer and burr are complementary, allowing the shaped metatarsal head to be jammed into the hollowed-out base of the proximal phalanx, and thus impacting the two bones firmly together. Firm fixation is obtained from a screw inserted obliquely across the joint.

These instruments have been produced for me by Messrs. Down Bros. and Meyer & Phelps Ltd., 32, New Cavendish Street, London, W.1, and the London Splint Co., 67, Weymouth Street, London, W.1.

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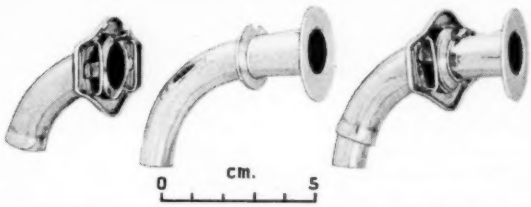
A MODIFICATION OF THE COLLEDGE LARYNGECTOMY CANNULA

DURING the first days after operations involving total laryngectomy the patient has to wear some form of rigid tube in the tracheostome to ensure a clear airway and give proper access for suction and toilet. A detachable inner component is essential to facilitate frequent cleaning without removal of the outer tube and dressings.

Since such a tube should extend forwards well clear of the inevitable heavy dressings, it usually has two perforated flanges set at right angles to the lumen. The first of these is attached to the tube at skin level, being kept in position by tapes, and the second is at the upper end to prevent dressings from falling across the orifice. For about 36 years these requirements have been met in this country by the Moure's modified or extended type of Lombard laryngectomy cannula. But, by reason of its



weight, length, and rigidity, this tube is unsatisfactory for continued use once the dressings are discarded. When a laryngectomy tube is required at this or any later postoperative stage, the shorter, lighter, and more suitable Colledge laryngectomy cannula is generally used.

Although satisfying basic requirements, the extended Lombard cannula is open to criticism because of its relative weight, single size, small calibre, and rigidity. The conical base at skin level was perhaps originally designed with the idea that constant pressure on the healing suture line would produce ultimate dilatation of the tracheal orifice. But the reverse effect may readily be produced, the pressure delaying healing at the mucocutaneous junction, with consequent fibrous contracture of the tracheal orifice.

In view of these disadvantages, and for the sake of economy and simplicity, it is useful to equip one of the three existing sizes of the Colledge cannula with an inner component, thus forming a composite laryngectomy tube. The inner component can be extended at either end to keep the airway open during the immediate postoperative period, when heavy dressings and frequent cleansing of the tube are essential. As soon as the sutures are out and dressings are no longer required, this inner tube may be discarded, and after a further short interval the outer tube may also be dispensed with in many patients.

To meet these requirements a flanged silver-alloy inner component, extended at both ends, has been designed to fit the standard medium size Colledge laryngectomy cannula (see figure). As shown, the cannula has also been fitted with a rotating catch on its upper margin to hold the inner component in place. This catch is not essential since an elastic band or strip of tape may be used to prevent the inner tube from being displaced during the short period of heavy neck dressings.

Specifications (for the medium size Colledge cannula) are:

Weight of whole composite tube	$1^1/_2$ oz. (2 oz.*)
Length of inner tube	8·8 cm. (9·0 cm.)
Length of outer tube	5·5 cm. (8·9 cm.)
Length of tracheal extension	1·1 cm. (0·1 cm.)
Length of surface extension	2·2 cm. (1·5 cm.)
Smallest internal diameter of inner tube	1·0 cm. (0·8 cm.)

Thus the composite Colledge tube is lighter and has a wider lumen than that of the Moure/Lombard pattern. A similar inner component has also been manufactured to fit the small size Colledge cannula, which is more suitable for women. This smaller model reduces still further the weight and bulk without impairing the efficiency of the airway.

The only practical points which have emerged from a thorough clinical trial are that the airway must be carefully watched when the inner tube is changed or cleaned, and that care must be taken to see that the inner tube is always fully inserted and secured. Attention to these points presents no great difficulty provided that the nurses are well trained in the postoperative management of such cases.

It is hoped that this inner component for the Colledge laryngectomy cannula will give a better airway with better healing of the tracheostome, greater comfort to the patient, and possibly more economic use of existing equipment.

Messrs. Down Bros. and Mayer & Phelps, Ltd., 32, New Cavendish Street, London, W.1, manufacture the inner component in the two sizes quoted.

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* Figures in parentheses are from the Moure/Lombard cannula for comparison.

Reviews of Books

A Textbook of Surgical Physiology

R. A. JAMIESON, M.B., F.R.C.S.E., surgeon, Vale of Leven Hospital; A. W. KAY, M.D., F.R.C.S.E., professor of surgery, University of Sheffield. Edinburgh: E. & S. Livingstone. 1959. Pp. 623. 55*s*.

HERE is a sign of the times—a sign which will not be missed by the new generation now reaching surgical maturity—for the fact that this book has been written is an acknowledgment of the shift in basic surgical outlook. Anatomy and the topography of technique are now less important for the surgical trainee than the repercussions not only of disorder but also of his own interventions. It could be argued with some justice that he who knows physiology intimately is safer than the expert in anatomy: there can be no guessing to make up for ignorance of biochemical principles when applying intravenous therapy, for instance, whereas the man who has to go down an unknown lane on a dark night at least has the opportunity of finding his way with the aid of a torch. This book is therefore of considerable importance since it has no exact forerunner; the information it contains could be gleaned from many sources, but it has not previously been brought together in this way. The conception of the whole work is as striking an achievement as its execution.

The temptation to include more than is immediately necessary for the practice of general surgery must have been considerable, but the authors have avoided it; and because the emphasis is on general surgery ovarian physiology, except in the relationship of its hormones to breast cancer, is omitted, as is the central nervous system. For the same reason, no doubt, readers are referred in a useful chapter on the heart to original sources for intimate details of heart-lung machines; though the mechanical principles of the artificial kidney are described succinctly but adequately in a later chapter on that organ. The style is brief and to the point, the cover comprehensive; the authors' apologies for inadvertent omission seems to have been superfluous. They have done a neat job and a fine work has now been added to others which have emanated from Glasgow to make surgical study more rational; and it is pleasing to note the credit given by the authors to the man who has done much to bring this about—Prof. C. W. Illingworth.

Heavy Metals and the Brain

JOHN N. CUMINGS, M.D., F.R.C.P., professor of chemical pathology in the University of London at the Institute of Neurology. Oxford: Blackwell Scientific Publications. 1959. Pp. 161. 32*s*. 6*d*.

THIS book is arranged in three sections: the first and largest is concerned with copper and hepatolenticular degeneration, and the other two deal with the nervous manifestations of poisoning by mercury and lead. Its thoroughness is indicated by the fact that, of the 150-odd pages of text, no less than 30 are devoted to a bibliography of some 900 references. Such a flood of references is a handicap to smooth literary composition, but the book is nevertheless highly instructive. Morbid anatomy and what might be called " gross chemical pathology " are fully described, together with clinical and therapeutic data. Less attention is given to biochemical mechanisms at the cellular level, and some general aspects of the relation of heavy metals to enzymes might have merited inclusion. Professor Cumings has undoubtedly provided an excellent source-book on the topics he has chosen.

Atlas of Roentgenographic Measurement

LEE. B. LUSTED, associate professor of radiology, University of Rochester School of Medicine; THEODORE E. KEATS, professor of radiology, University of Missouri School of Medicine. Chicago: Year Book Publishers. London: Interscience Publishers. 1959. Pp. 176. 68*s*.

EXPERIENCED radiologists base their judgment largely on appearances, but the statement that " it appears normal " often seems lame and unconvincing to clinical colleagues and students. This atlas aims to help radiologists in such circumstances. The authors have tabulated from published data and from their own work, the average size and normal variation of most of the measurable body structures. Amongst the more useful features are measurements of the cerebral ventricles and the position of the cerebral vessels as seen by arteriography. The relationships of all the major joints should prove particularly valuable, especially when assessing congenital subluxation of the hip and abnormalities around the ankle-joint. The text includes the standard radiographic positions by means of which such measurements can be made. Many pages are devoted to the various measurements of the heart, female pelvis, and fœtal head, and there are excellent tables on the maturation of the skeleton.

Fear, Punishment, Anxiety and the Wolfenden Report

CHARLES BERG. London: Allen & Unwin. 1959. Pp. 120. 20*s*.

ONE of the late Dr. Charles Berg's exceptional gifts was his ability to explain difficult concepts in terms that ordinary people could follow; and this despite the fact that many of the things he understood well are rather apt to provoke resistance in readers. The four essays in this book are of his usual high standard. The first is a critical evaluation of that part of the Wolfenden Report which deals with homosexuality. In terms of great severity, he criticises both the methods and some of the conclusions of the committee. Resignations, minority reports, and reservations, all taken as disagreement amongst themselves, are explicable to the analyst only as the inevitable result of personal ignorance. But some of the recommendations are praised and the fact that the committee has shed a great deal of light into dark places is acknowledged.

Berg's second essay, on the psychology of punishment, is an admirable contribution, in which punished and punisher are discussed in terms of the unconscious forces that shape belief and conduct. We trace the footsteps of the Roman citizen enjoying the spectacle of criminals being thrown to the lions, or being publicly castrated, down to the present day with its emphasis on psychological suffering and find it is we ourselves who stand in the Roman's shoes. " Punishment *means* destruction . . . why delude yourselves " the author asks disturbingly.

The last third of the book is devoted to an attempt at understanding the nature of anxiety and fear. This makes harder reading and is rather speculative in places. The whole book is interesting and rewarding, not least for those whose chief concern lies outside present psychological thought.

Honour a Physician

PHILIP AULD. London: Hollis & Carter. 1959. Pp. 270. 16*s*.

IN form an anecdotal narrative, this book is in effect a bitter and sustained indictment of the National Health Service as a corruptor, primarily of patients, secondarily of doctors, and a destroyer of family doctoring, good clinical medicine, and continuing medical care. It has long been known that some citizens are devoid of citizenship and respect for truth and that a minority lack manners or decency of any kind. The indictment's chief count is that to these people has been given the right to demand visits of their doctors at any hour of the year without cost to themselves or penalty for abuse. The doctor's only remedy is to have incorrigible offenders removed from his list, thereby dumping them on his neighbours. Gluttony for certificates and medicines is stimulated; good patients become shy of seeking the help they need.

" Dr. Gatwood " has a social and a medical conscience, his heart is in his job, he welcomed the Service; but ten years of buffeting at the hands of patients, without help or recognition of his plight by Ministry, Parliament, Press, or B.M.A., drives him, reluctant, out of the Service into part-time industrial medicine and private practice. Some of his colleagues beat less honourable retreats.

The book demands earnest attention by the profession and by those in authority over the National Health Service, for the picture it paints is one that many people believe to be truly drawn.

THE LANCET
LONDON 16 JANUARY 1960

Toxæmia of Burns

EXTENSIVE burning is followed by serious illness and, despite advances in therapy, many patients still die. The general effects are so profound that it is not surprising that an embracing concept of toxæmia or autointoxication was put forward many years ago. The idea is said [1] to have originated in 1876 in Petrograd, where AVDAKOFF reported that the blood of burned animals was toxic to others. Toxic products released from the burned skin or the blood are alleged to produce illness and even death; but the number and variety of the toxins isolated from time to time (toxalbumin, ptomaines, formic acid, ammonia, proteoses, peptones, histamine, methyl guanidine, hydrocyanic acid, and many others) indicates either their multiplicity or their elusiveness. At one time the concept led to the treatment of burns by tanning, which, by precipitating the proteins in the altered skin, was said to prevent absorption of their "toxic" products; but the tannic-acid treatment itself produced toxic effects, and tanning—or at least tannic acid—is now discredited. The concept of autointoxication held the field for over fifty years; but during the last twenty to thirty of these years it lost much ground, mainly because advances in physiological and pathological knowledge of burns have rendered the theory less and less necessary and have led to the introduction of life-saving therapy—especially plasma-transfusion, antibiotics, and skin excision and grafting.

The main facts about the hæmodynamic nature of burn "shock" and its relation to oligæmia have now been established. Oligæmia is brought about mainly through the loss from the blood into the acutely inflamed burned area of large quantities of a plasma-like exudate; the redistribution of body-water is associated with changes in proteins and electrolytes which can lead to hypoproteinæmia, sodium depletion, and dehydration; renal failure and changes in the kidney are due to a lowered filtration-rate and renal ischæmia, and are accentuated by hæmoglobinuria; the hæmoglobinuria is due to acute red-cell destruction which produces red-cell oligæmia and anæmia and occasionally hæmolytic jaundice; whilst biochemical and metabolic disturbances involving carbohydrates, nitrogen, minerals, and vitamins are brought about by humoral or neurohumoral mechanisms in which the adrenal gland and especially adrenocortical hyperactivity are involved. The burned skin rapidly becomes contaminated with bacteria of which *Streptococcus pyogenes*, *Pseudomonas pyocyanea*, *Staphylococcus aureus*, proteus, and various coliform bacilli are the most important; transient or intermittent bacteræmia is common, and not uncommon are septicæmic invasion and pneumonia; these are often responsible for "toxæmic" pyrexia, illness, and death, particularly in those surviving the first few days. Nevertheless there is still no complete explanation of many effects of burning, such as the early hyperæmia of the lungs, stomach, bowel, kidneys, and other organs, early hyperpyrexia, and polypnœa; and many patients still die despite energetic medical and surgical therapy. Although nearly all very extensively burned patients can be kept alive for a week or longer by modern fluid therapy, some die later—generally from pneumonia, other bacterial infection, or other causes which are sometimes obscure. Are some deaths due to non-bacterial toxæmia?

If burn toxæmia is real it is certainly a less embracing cause of illness and a less important cause of death than was once believed. Experimental findings are voluminous but conflicting. Severe illness or death in normal animals has been observed after injection of extracts of burned skin or exudate [2–4] or the blood or serum of burned animals,[5–7] but other workers [1 8–11] have found no deleterious effects. Some of these reports are likely to be invalid because there is doubt about the sterility of the material injected and bacteria may have been responsible. Cross-circulation experiments [12–15] between burned and normal animals in which the normals became ill or died do not necessarily denote that a toxin was transferred from one animal to the other, because oligæmia in both animals could explain the results; while the beneficial effects of exclusion by ligation or excision of the burned part soon after burning [1 14 16 17] can just as well be explained by the prevention of gross burn œdema and consequent oligæmia. Nevertheless various substances are undoubtedly released or newly formed after burning.[18] These include hæmoglobin, potassium, nuclear nucleoprotein,[19] adenosine,[20–22] phosphate, and pentose, probably ribonucleic acid, abnormal proteins [23] including gelatin,[24] polypeptides (some with leukotaxic properties [25]), histamine,[24 26 27] and glycoprotein.[28] Some of these are formed in or released from the burned skin and were detected in the skin or the local œdema fluid or the lymph draining the burned area, while others are released from heat-altered red

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cells. The liberation of a skin proteinase [29] by heat-injured epidermis, the activation of other proteolytic enzymes,[30] and the release of peptidases [31] probably account for the proteins in the exudate. Skin proteinase, polypeptides, and possibly other products may play a chemical intermediary part in producing, or (as SEVITT [32] suggested) more likely maintaining, the œdema of burns.

The idea of toxæmia is being kept alive through the work of SIMONART, GODFRAIND, and their colleagues in Belgium, ROSENTHAL and his colleagues in the U.S.A., and FEDEROV and his colleagues in the U.S.S.R. SIMONART, whose work dates back to 1928, has summarised his experience.[33 34] In laboratory animals he divides the course following burning into three overlapping phases: (1) *choc circulatoire précoce* (from generalised capillary dilation); (2) *déshydration;* and (3) *autointoxication*, which he believes is due to absorption of hydrolytic products of protein in the œdema fluid. Not only was œdema fluid found to be toxic or lethal after injection, but various fractions extracted from the fluid, including euglobulin and peptones, had toxic or lethal effects. That œdema fluid from burned rabbits is toxic to normal rabbits was established by WILSON et al.[4] in Edinburgh in 1936 and was later confirmed by CULLUMBINE et al.[35] in Manchester; but the lethal intravenous dose for rabbits was as much as 10 ml. of exudate per kg. body-weight, and for mice it was still more.[36]

The work of SOL ROSENTHAL (not to be confused with SANDFORD ROSENTHAL, who also works on burns) dates back to 1937; and he too has summarised his latest work.[37] Diffusates from burned skin, obtained both in vitro [24 26] and in vivo,[37 38] were studied.

The in-vivo diffusate (œdema fluid) contained protein, protein split-products, sugars, salts, histamine, bradykinin, adenyl compounds, and other substances. Injection of the fluid obtained from the burned skin of rats was lethal to other rats and to mice, and the speed of dying depended on the dose and route of administration. The toxic property was heat-stable, dialysable (i.e., non-protein) and partially precipitated by 80% ethyl alcohol; the toxic dialysable fraction contained peptides, polynucleotides, hexoses, and pentoses. Histamine, bradykinin, and adenyl compounds were not related to this burn " toxin ".

Thus both the Belgian and the American work on burn œdema supports the concept originally put forward by PFEIFFER [6 7] that toxæmia is due to the formation of degradation products of proteins. If this is correct, and if proteins and local products of proteolysis also play a part in producing burn œdema, then the pathogenesis of burn inflammation is closely linked to the origin of toxæmia. Of course the agents concerned would not be specific for burns; similar " toxins " would be formed in any inflammatory condition of the skin and probably other tissues, and the " toxæmia " would be a general disorder. This would be an important link between, on the one hand, burn inflammation and toxæmia, and, on the other hand, peptides and serum-proteins which have been reported to act as chemical mediators of altered capillary permeability in other forms of experimental inflammation.[39–44] Whether the toxicity of œdema fluid found experimentally is clinically important depends on whether the toxic products enter the circulation (this seems likely), how quickly they enter, how and how quickly the body deals with them, and their rate of destruction and elimination. Experimentally, it is important to establish whether in-vivo inhibition of local proteolysis by drugs or other means can reduce the toxicity of œdema fluid.

The work of FEDEROV [45 46] and his colleagues in the U.S.S.R. is different. They have extended the search for toxins into the interesting field of autoimmunisation. Autoimmunisation might explain certain obscure features, such as delayed eosinophilia after burning,[47] which might result from sensitisation following the absorption of altered proteins in the burned area. FEDEROV holds that the body is flooded with antigens derived from the burned skin and that this is responsible for part of the burn illness; and that the subsequent autoimmunisation is a regular sequel of burning. Certain antigens found in the blood and tissues of burned dogs were serologically similar if not identical with those in the burned skin; they were present in the circulation one or two days after burning and were detectable for up to fifteen days. Skin antigens in blood were detected by immunisation of normal guineapigs with the serum of dogs taken at various times after burning. Antibodies developing in guineapig serum after absorption of the serum with dog serum removed before burning were identified, using extracts of burned dog-skin as the source of antigen. Autoantibodies appeared in the circulation after the antigens had disappeared; and this raises hopes for therapy. Complement-fixing titres of the order of 1 in 640 were found for saline extracts of burned skin six or seven weeks after burning. The serum from dogs which had recovered from burns produced beneficial results in other burned dogs. Moreover the sera of healthy dogs previously injected with blood from recently burned dogs (presumably containing skin antigens) had a pronounced therapeutic effect apparently greater than that of serum from non-immunised animals. Serum from convalescent burned patients given in doses of 250 ml. daily for three or four days to recently burned patients (as a supplement to other intravenous therapy) was said to have clinically impressive results. FEDEROV believes that the sera injected were immune sera containing antibodies against toxic antigens liberated from burned skin, and that the

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30. Ungar, G., Damgaard, E. *Proc. Soc. exp. Biol., N.Y.* 1954, **87**, 378.
31. Zamecnic, P. C., Stephenson, M. L., Cope, O. *J. biol. Chem.* 1945, **158**, 135.
32. Sevitt, S. *J. Path. Bact.* 1958, **75**, 27.
33. Simonart, A. *Bull. Acad. Méd. Belg.* 1957, **22**, 231.
34. Simonart, A. *Sem. Hôp. Paris*, 1958, **34**, 777.
35. Cullumbine, H., McDonald, F., Simpson, M. M. *J. Path. Bact.* 1947, **59**, 467.
36. Godfraind, T. L'auto-intoxication après brûlure. Brussels, 1958.
37. Rosenthal, Sol. R. *Surgery*, 1959, **46**, 932.
38. Rosenthal, S. R., Hunter, F. R., Hunter, A. S., Finamore, F. J., Williams, F., Roman, I. *Fed. Proc.* 1955, **14**, 124. Rosenthal, S. R., Finamore, F. J., Hunter, F. R., Williams, A. D. *ibid.* 1956, **15**, 156.
39. Menkin, V. *J. exp. Med.* 1936, **64**, 485.
40. Duthie, E. S., Chain, E. *Brit. J. exp. Path.* 1939, **27**, 33.
41. Spector, W. G. *J. Path. Bact.* 1951, **63**, 93.
42. Wilhelm, D. L., Miles, A. A., Mackay, M. E. *Brit. J. exp. Path.* 1955, **36**, 82.
43. Miles, A. A., Wilhelm, D. L. *ibid.* p. 71.
44. Spector, W. G. *J. Path. Bact.* 1956, **72**, 367.
45. Federov, N. A. *Congr. int. Soc. Blood Transf.* 1956, p. 54.
46. Federov, N. A. Report to 7th European Congress on Hæmatology, 1959.
47. Sevitt, S. *Brit. med. J.* 1951, i, 976.

protective effect was partly or largely due to neutralisation of the flood of toxic antigens. Some of the beneficial effect may be due merely to the injection of serum per se or to its containing antibacterial antibodies arising after infection of the burn. Obviously confirmation and further work are necessary because of the hope of improving therapy and of saving some of those who at present succumb to extensive burns.

Dental Caries

IN a Bill of Mortality for London for one week in August, 1665, the cause of 118 deaths is given as "Teeth",[1] and for the whole of that year no less than 2614 deaths were ascribed to "Teeth and Worms"[2]; but as this was during the Great Plague, when endeavours were often made to conceal the true cause of death, the diagnoses are unlikely to have been particularly accurate. Dental caries is not in fact a killing disease, and research into its pathology and prevention has no dramatic appeal. Nevertheless it is responsible for much suffering, loss of working-time, and, quite possibly, chronic ill health.[3] The principal school dental officer for Derbyshire said recently: "Already there are children in the older age groups of school who are toothless and wear full sets of dentures, while hundreds more will be in a similar condition in a year or two after leaving school."[4] And efforts at prevention are not always rational when, as TOLLER ruefully observes,[5] films directed at the iniquity of eating the wrong foods between meals are shown to schoolchildren on projectors bought out of the profits of the school tuck-shop.

On the pathology, DARLING[6] makes it clear that, despite a fair amount of agreement about many of the processes in the development of caries, we do not fully understand what takes place and the reasons. It is a tribute to W. D. MILLER that his "chemicoparasitic" hypothesis, first described in 1890,[7] is still accepted with slight modifications that concern mainly the role of the dental micro-structure. There can be little doubt that caries is predominantly a local process: although systemic factors can affect the tooth structure during development, they are not likely to produce any change in the enamel after eruption. Similarly, while the composition of the saliva may have some slight effect on the process of decay, it is unlikely to exert more than a modifying influence. Caries originates in the bacterial fermentation of refined carbohydrates retained in stagnation areas around the teeth, and this fermentation produces some agent that attacks the enamel. What this agent is has not been determined—it could be an acid, a substance causing proteolysis, or a chelating agent. A proteolytic substance seems to be the least likely of the three, since proteolysis has not been demonstrated until fairly late in the carious process. There is, however, a good deal of evidence that lactic acid may be responsible. Lactic acid is found in stagnation areas; carious enamel contains an abnormal amount of lactate; dilute lactic acid will produce lesions resembling those of natural caries; and lactic acid can act as chelating agent.

Dental caries is a complex process—rather is it a chain of processes determined by several factors. In theory the elimination of one of these factors should interrupt the sequence, but in practice no one method has prevented caries completely. The great significance of the accumulation of refined carbohydrates in the stagnation areas around the teeth has been shown by GUSTAFSSON et al. in Sweden.[8] The oft-expressed opinion that one specific organism is responsible for carbohydrate fermentation in the mouth seems to be untenable (and certainly this did not form a part of MILLER'S original hypothesis). *Lactobacillus acidophilus* is found in association with caries; but the disease has been produced artificially both with a streptococcus and with an enterococcus. The importance of the structure of the tooth was almost neglected until the publication in 1934 of the work of MELLANBY,[9] which showed a connection between minor enamel hypoplasia and the incidence of caries. The structure of enamel is still imperfectly understood, but it exerts a great influence on the development of caries. Properly developed enamel has a highly resistant surface zone, some 30 μ thick[10]—which is important in prevention, since this zone may easily be abraded during conservative treatment of adjoining teeth.

Caries in the enamel progresses by selective decalcification, certain parts of the micro-structure being attacked first; and at present the only reasonable explanation seems to be that this is associated with the distribution of soluble and insoluble proteins in the enamel. About equal amounts of each type of protein are present in the interprismatic spaces,[11] and the soluble protein is assumed to be the first part of the tooth substance to disappear. The situation is now complicated by the work of HELMCKE,[12] which suggests that the interprismatic spaces may be optical illusions. From electron microscopy of enamel he concludes that these spaces are produced by the refraction of light along the optic axes of the hydroxyapatite crystals forming the prisms. Since it is highly improbable that these axes would all be parallel, the resulting system of optical lenses could produce—in a light microscope—the appearance of dark areas which do not in reality exist.

To quote Professor DARLING: "If we are to prevent caries we must seek to break the chain of processes which cause the lesion." Of the various means available to the dentist, none is wholly effective. Stagnation of food around the teeth can be reduced, but not eliminated, by intelligent and efficient brushing. To induce patients to reduce their intake of refined carbohydrate is very difficult; but something can be achieved by limiting the intake of carbohydrates strictly to mealtimes, and to the half-hour immediately afterwards, provided this

1. Haggard, H. W. Devils, Drugs, and Doctors; p. 192. New York, 1929.
2. Gale, A. H. Epidemic Diseases; p. 151. London, 1959.
3. See *Lancet*, 1951, i, 1009.
4. *Times*, Sept. 11, 1959.
5. Toller, J. R. Memorandum to City of Cambridge Education Committee, Dec. 10, 1959.
6. Darling, A. I. *Brit. dent. J.* 1959, **107**, 287.
7. Miller, W. D. The Micro-organisms of the Human Mouth. Philadelphia, 1890.
8. Gustafsson, B. E., Quensel, C-E., Lanke, L. S., Lundqvist, C., Grahnen, H., Bonow, B. E., Krasse, B. O. *Acta odont. scand.* 1954, **11**, 232.
9. Mellanby, M. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1934, no. 191.
10. Applebaum, D. *J. dent. Res.* 1932, **12**, 619.
11. Stack, M. V. *J. Amer. dent. Ass.* 1954, **48**, 297.
12. Helmcke, G. *Umschau.* 1959, **17**, 516. Cited by *New Scientist*, 1959, **6**, 709.

is followed by attention to oral hygiene. Antiseptics can render the mouth almost sterile for short periods, but are soon dispersed and diluted by the saliva. Artificial immunity has been produced but is only ephemeral. Enzyme inhibitors have been tried,[13] apparently with some initial success, but little has been heard of them in the past decade. A more promising, though empirical, method is the administration of pyridoxone (vitamin B_6)[14]; but this has not yet been established as a practical means of control. The neutralisation of lactic acid as it is formed presents the same difficulties as in making the oral cavity sterile: it is almost impossible to modify the composition of the saliva. Rendering the soluble protein of the enamel insoluble might prevent a great deal of caries—a possibility which is now being investigated. The use of silver nitrate has little scientific backing, and yet clinical experience shows that it is often effective.

But neither the ramifications of research nor the skilful expedients of dentistry should distract attention from the most important fact about caries—that it is a consequence of malnutrition and that we already know enough to prevent nearly all of it. In his fascinating review of the changes in its incidence and distribution in this country throughout the ages, HARDWICK [15] relates these to changes in our diet, which have been greater in the past hundred and fifty years than ever before. When a disease goes up and down with alterations in feeding, it is obviously a soluble problem of public health; and, though HARDWICK is not prepared to say which of the many nutritional alterations of the 19th and 20th centuries is chiefly responsible for caries, he shows that all the more likely factors are related to refining of foods. Most conspicuous, perhaps, is the loss of most of the components which promote mastication and natural cleansing of the teeth. Next there is the large consumption of refined sugars, which (together with heating of our homes and lessening of our physical activity) has reduced the intake of old-fashioned foods containing possibly protective factors such as vitamins and trace elements. Likewise the concomitant modifications of the processing of flour " have been followed by marked changes in caries activity ". Changes in the incidence of the disease during and after the two world wars suggest that there are (or should be) factors in food whose absence during a tooth's formation makes it susceptible to caries later. " An increasingly large group of research workers believes . . . that these protective factors are of an inorganic nature and it has been suggested that caries may be a trace element deficiency disease."

The day may be far distant when the public can be weaned from its present somewhat infantile overdependence on refined sugar and fat: indeed there are hardly any signs yet that doctors and dentists care enough about nutrition to set their weight firmly against the commercial interests concerned. Meanwhile, though perhaps a pis-aller, the correction of fluorine deficiency seems to be our most hopeful objective. Where water-supplies are clearly below normal in fluorine content, any reasonable person should be willing to accept the minute addition of fluoride needed to make up for the geological lack. Doing no more than this has sometimes reduced the local incidence of caries by as much as half.

13. Fosdick, L. S., Calandra, J. C. *J. dent. Res.* 1947, **26**, 309.
14. Strean, L. P., Bell, F. T., Gilfillan, E. W., Emerson, G. A., Howe, E. E. *N.Y. St. dent. J.* 1958, **24**, 133.
15. Hardwick, J. L. *Brit. dent. J.* Jan. 5, 1960, p. 9.

Annotations

FERTILITY CONTROL

IF man's most pressing task is to escape total destruction by nuclear warfare, the next most urgent is to feed and clothe his ever-increasing family.[1] Economists since the days of Malthus have insisted that measures to increase food production are bound to prove increasingly ineffective as time passes. Fertility, according to this viewpoint, must be controlled, though without prejudicing the health and welfare of the individual or the race. This simply stated goal is proving difficult to attain—a fact that testifies to the long course of evolution in which mammals have been developing means for protecting sex cells and embryos from environmental interference.

Reproduction can be blocked in broadly two ways: by preventing the production and union of sex cells; and by bringing about, directly or indirectly, the death of the embryo. It is now agreed that ideally contraception should be applied by oral administration of the active agent, and specifications for an ideal contraceptive have been drawn up.[2] Some of the latest products of the search for a suitable agent were discussed by Dr. H. Jackson in an address to the Pharmaceutical Society on Dec. 3.

Dr. Jackson is well known for his studies on several groups of organic compounds, notably the ethyleneimino derivatives, one of which is tretamine (T.E.M.). Administered in a single moderate dose to male rats, this damages the late spermatids but not the earlier spermatogenic cells nor the maturing spermatozoa. As a result, the rats become sterile between the 20th and the 26th days after treatment, though they are fertile before and after this period. At higher dose levels, the damage extends to other stages of spermatogenesis, involving spermatogonia and maturing spermatozoa.[3–5] Similar results have been obtained with mice.[6] The action of tretamine, besides being remarkably cell-specific, is notable in that it renders the epididymal spermatozoa infertile without inhibiting their motility or their ability to reach and enter the eggs.

Another group of compounds discussed by Dr. Jackson was the sulphonoxalkanes, such as busulphan (' Myleran '). Here again, damage tends to be concentrated at specific stages of spermatogenesis: with busulphan on the spermatogonia; with chloroethylmethanesulphonate on the spermatids and spermatozoa; and with dimethylmyleran on both groups of cells.[4] With these and other compounds of the same family, it is evidently possible to build up a " spectrum " of activity, wherein variations in effect accompany relatively small differences in chemical structure. These drugs can yield precise data on the course of spermatogenesis and on the physiological and chemical peculiarities of the spermatozoon. But whether they can suitably be applied to the control of fertility in

1. See *Lancet*, 1959, ii, 389.
2. Parkes, A. S. *Proc. Soc. Study Fertil.* 1953, **5**, 20.
3. Bock, M., Jackson, H. *Brit. J. Pharmacol.* 1957, **12**, 1.
4. Jackson, H., Fox, B. W., Craig, A. W. *ibid.* 1959, **14**, 149.
5. Steinberger, E., Nelson, W. O., Boccabella, A., Dixon, W. J. *Endocrinology*, 1959, **65**, 40.
6. Cattanach, B. M. Edwards, R. G. *Proc. roy. Soc. Edinb.* **B**, 1958, 54.

man is another matter; for they are known to be capable of producing changes in the genetic material of the spermatozoon,[6 7] and for other reasons, too, may be classed as radiomimetic agents.[8] Substances which have these effects, but which do not prevent the spermatozoon from entering the egg, cannot be regarded as any less hazardous than atomic radiation and should be treated with the same reverence.

Dangers of somewhat lower degree, though still serious, attend practices that depend on destruction of the early embryo. Here, too, phenomenal specificity of chemical action is manifest, notably in the lethal effect of the triphenylethanol derivative known briefly as MER-25 on the unimplanted embryo [9] and that of podophyllotoxin after implantation.[10] This work represents a fascinating aspect of experimental biology; but there is an ever-present risk that the embryos may not all be killed and that damaged embryos may survive to term.

Some lines of research seem to offer hopes of satisfactory results with comparative safety: these depend on suppression of ovulation or of implantation. The best known is the oral administration of certain 19-nor steroids with progestational activity which apparently inhibit the gonadotrophin output from the pituitary.[11] Hopeful also are the results with *m*-xylohydroquinone [12 13]; this substance is believed to inactivate gonadotrophin, œstrogen, and progesterone in vivo by combining directly with them. In the suppression of implantation, some success has been reported in rats treated with ergotoxine,[14] but the most innocuous method of achieving this effect has recently been observed in mice: pregnancy was interrupted at high frequency by no more drastic an expedient than allowing the females to become aware of the proximity of strange males.[15 16]

TREATMENT OF INFECTIONS IN HOSPITAL

In the past twenty-five years sulphonamides, penicillin, antituberculous drugs, broad-spectrum antibiotics, various antistaphylococcal agents, and some promising antifungal substances have become available. Nevertheless, infective disease remains undefeated and some types are on the increase. The lamentable lack of achievement has been exposed by Finland and his colleagues [17] in an authoritative report to the Council on Drugs of the American Medical Association. These workers have reviewed the changing pattern of infections observed in the Boston City Hospital in certain years, carefully chosen to reflect the changing fashion in chemotherapy. The year 1935 was selected as a baseline for the pre-sulphonamide era; 1941 to reveal the impact of the sulphonamides before they had been joined by penicillin; 1947 when both penicillin and streptomycin had been widely used; 1951 to show the influence of the broad-spectrum antibiotics; and 1957 to define recent trends influenced by most or all currently available antibiotics. In order to make valid comparisons, attention was restricted to septicæmia, meningitis, empyema, and necropsy material from which bacteriological studies were satisfactory.

In 1935 about 300 septicæmic patients were admitted to hospital and roughly three-fifths of these died. By 1957 there were twice as many septicæmic patients, nearly two-fifths of whom died: whereas 2 out of 5 septicæmic patients could be saved in the dark ages before sulphonamides, no more than 3 out of 5 survive with the help of modern chemotherapy. The decline in mortality occurred in the years 1935–41, when the sulphonamides were in exclusive use, for by 1941 only one-third of septicæmic patients died. Since then and, with the use of penicillin, streptomycin, and the broad-spectrum antibiotics, the mortality-rate has increased.

In contrast, meningitis and empyema have become rather less of a challenge. As regards meningitis, there were rather more cases in 1957 than in 1935, but between these years the mortality had steadily fallen from 80% to 20%. Between these particular years the number of patients with empyema had halved, although the mortality rate had risen slightly from 20 to 30%.

The bacteria isolated from these infections have changed significantly over the years, and this changing flora mirrors the success and failure of the antibiotics. Pneumococci and hæmolytic streptococci have continued to remain sensitive to antibiotics, but success in this direction has been offset by the increasing incidence of infection due to staphylococci, enterococci, and various gram-negative organisms, against which existing drugs are less potent. The mortality-rate of septicæmia due to gram-positive organisms was 67% in 1935 and 33% in 1957. The fall in mortality would have been far more impressive but for staphylococcal infections, whose incidence quadrupled over these years. The incidence of septicæmia due to gram-negative organisms increased sixfold, and the mortality also rose slightly from 42% (1935) to 54% (1957). In essence, the antibiotic era has witnessed a change from pneumococcal to staphylococcal and coliform septicæmia. The gravity of the staphylococcal menace is reflected also in the frequency with which this organism was isolated in pure or almost pure culture from one or more important sites in necropsy material. It was recovered from 7% of necropsies in 1935 compared with 24% in 1957. Finland and his coworkers draw attention to this as a crude index of the increasing significance of *Staphylococcus aureus* as a cause of death.

This survey might be interpreted less confidently had it not been made at the Boston City Hospital—a large general city hospital, admitting 4 patients every hour round the clock, where throughout the years covered by the survey Dr. Maxwell Finland has himself been responsible for the management of infections.

Possible steps to reduce the hazard of infections include vigilance against cross-infection, combination of antibiotics, rotation of drugs, limitation of the use of some, the introduction of fresh antistaphylococcal agents, and new measures to improve host resistance. That the challenge has been accepted in London is evident from the painstaking work of Barber and her colleagues [18] and the cooperation of the whole staff of Hammersmith Hospital, where some reversal of antibiotic resistance in hospital staphylococcal infection has already been achieved by the introduction of some of these measures in the surgical wards. At the beginning of the investigation, 70% of staphylococcal infections were resistant to penicillin and tetracycline and only 12% were sensitive

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10. Wiesner, B. P., Yudkin, J. *Nature, Lond.* 1955, **176,** 249.
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12. Sanyal, S. N. *J. Med. intern. med. Abstr.* 1959, **23,** 15.
13. Sanyal, S. N., Rana, M. *ibid.* p. 33.
14. Shelesnyak, M. C. *Recent Progr. Hormone Res.* 1957, **13,** 269.
15. Bruce, H. M. *Nature, Lond.* 1959, **184,** 105.
16. Bruce, H. M. *J. Reprod. Fertil.* (in the press).
17. Finland, M., Jones, W. F., Barnes, M. W. *J. Amer. med. Ass.* 1959, **170,** 2188.
18. Barber, M., Dutton, A. A. C., Beard, M. A., Elmes, P. C., Williams, R. *Brit. med. J.* Jan. 2, 1960, p. 11.

to penicillin. At the end of the investigation, 36% of the infections were resistant to penicillin and tetracycline and 48% were sensitive to penicillin. The use of penicillin was deliberately restricted, and broad-spectrum antibiotics in combination were used more freely. The consumption of penicillin in the hospital was halved, but that of tetracycline, chloramphenicol, and erythromycin doubled, and the use of novobiocin increased sixfold. The increased cost entailed by this programme is unimportant if it succeeds. One peril is that gram-negative organisms may become increasingly often resistant to the broad-spectrum antibiotics. It would be difficult to defend the unlimited use of polymyxin for bacillary dysentery and trivial skin infections in a hospital, if this involved an increase in infections with resistant pseudomonas for which originally only polymyxin is effective. This organism alone was responsible for 13 deaths in 1957 in the Boston City Hospital, compared with none in 1935. Barber and her coworkers are well aware of this danger; and, in re-shaping their policy for the next phase of the attack on hospital infection, they might even include the coliform organisms with staphylococci as their quarry.

CLASSIFICATION OF PSYCHIATRIC DISORDERS

DISCOVERING the prevalence of mental disorders in different communities helps both to throw light on their causation and to plan the therapeutic services. Minor psychiatric illness is much commoner than is usually realised, both as " maladjustment " in children [1] and in adults consulting their family doctors [2]; and outpatient facilities must be planned to meet the need. Arentsen and Strömgren [3] have reported a survey based on a census of all persons resident in Danish psychiatric institutions on a day in the autumn of 1957. The prevalence of such patients—228 per 100,000—was considerably less than the 342 per 100,000 in this country and the 430 per 100,000 in Sweden; and this was presumed to be due to nosocomial factors rather than to differences in morbidity. Sweden has been able to provide more hospital beds than Denmark and Norway (where the rate is also low), and geographical factors make outpatient management easier in Denmark. Distribution of diagnostic subgroups did not, overall, differ greatly throughout the country; but diagnostic practices in certain hospitals were strikingly discrepant, reflecting the present unsatisfactory state of classification. In her survey of mental illness in London, Vera Norris [4] found similar differences. In some conditions the concordance of diagnosis for the same patient between observation ward and mental hospital was less than 30%. Agreement on schizophrenia and manic-depressive psychosis, however, was about 70%, and the difference between the diagnoses was borne out by the very highly significant ($P < 0{\cdot}0001$) differences in duration of stay. Prof. Erwin Stengel [5] has surveyed 58 current classifications at the request of the World Health Organisation. He found that none was wholly satisfactory and most were bedevilled by national and personal sentiment. Despite minor difficulties with cardiovascular classification [6] the International Classification of Diseases has been generally accepted throughout the world except for the psychiatric section. Disagreement on definition has led to gross discrepancies in use, and Professor Stengel maintains that an acceptable classification demands that grouping be exhaustive and the categories mutually exclusive with each explicitly defined. That the present system has failed is made clear by Miss Eileen Brooke.[5] The I.C.D. and the American Psychiatric Association classifications are theoretically interchangeable, but when some 200 diagnoses were coded on each separately and the A.P.A. coding was used to give an I.C.D. code number, there was concordance in only a minority. Cohort analysis of cases discharged and readmitted elsewhere within four years showed a similar minority of concordant diagnoses. Miss Brooke concluded—as did Dr. Norris from similar findings—that only with the broad groupings did diagnosis seem " not completely haphazard ".

This unsatisfactory situation is hindering progress.[7] Pending the evolution of objective indices, we can only await the outcome of W.H.O.'s endeavours and hope that the conclusions will prove universally acceptable. Fortunately the planning of our future services need not wait on these deliberations; Professor McKeown and his colleagues, for example, have described a very useful system of classification, based on the treatment needs of patients, which ignores diagnosis.[8 9]

PULMONARY ARTERIOVENOUS FISTULA IN HEREDITARY HÆMORRHAGIC TELANGIECTASIA

EVERY large general hospital is certain to have on its list of frequent attenders a small group of unfortunate adults who come to the casualty department complaining of recurrent bleeding from the nose or lips or mouth. The blood is seen to stem from an insignificant leak in the centre of a small ruby patch, many of which are usually to be found scattered here and there on the mucous membrane. Although the flow of blood is seldom vigorous it may eventually, by its persistence, cause some concern. Its arrest can certainly be infuriatingly difficult, whether it be attempted by sustained compression or by cautery, or by both. Each ruby patch marks the position of a tiny arteriovenous communication at the capillary level. Presumably these vessels are very close to the surface, or else they are abnormally fragile. Whatever the cause, they can be induced to bleed by the most trivial of injuries.

This vascular anomaly is not restricted to the mouth and nose, but may affect any portion of the skin of the trunk. Similar lesions can also involve mucous membrane elsewhere; and bleeding from the gastrointestinal tract or hæmaturia often feature in the history. The disease is known to be hereditary and is presumed to be transmitted as a simple dominant with equal frequency by males and females. Most have now agreed to call the disease hereditary hæmorrhagic telangiectasia, but some students and compilers of texts still delight in the eponymous prolixity of Rendu-Osler-Weber disease.

Arteriovenous shunts in the lesser circulation, between branches of the pulmonary artery and of the pulmonary vein, were recognised at necropsy at the turn of the century, but it was not until 1939 that the first case was diagnosed clinically.[10] The triad of cyanosis, poly-

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2. Shepherd, M., Fisher, M., Stein, L., Kessel, W. I. N. *Proc. R. Soc. Med.* 1959, **52**, 269.
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4. Norris, V. Mental Illness in London: Maudsley monograph no. 6, 1959.
5. Stengel, E. Address at a meeting of the Section of Psychiatry, Royal Society of Medicine, Nov. 10, 1959.
6. See *Lancet*, Nov. 14, 1959, p. 836.
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cythæmia, and clubbing, which are the clinical features of the more serious shunts, is now widely recognised. Only in more recent years has it been widely appreciated that the great majority of patients with pulmonary arteriovenous fistulas will be found on careful examination to have, in addition, the characteristic lesions of hæmorrhagic telangiectasia. Purriel and Muras [11] in an analysis of 170 reported cases found that, of 102 patients concerning whom full information was available, 70 had cutaneous telangiectasia and that in close on 60% there was a family history of the disease. It seems clear, therefore, that we must now regard pulmonary arteriovenous fistulas not as localised lesions but as part of a general vascular anomaly, and that we must for this reason seek out other vascular deficiencies in seeking supporting evidence of a pulmonary arteriovenous shunt.

How many patients who present with evidence of hæmorrhagic telangiectasia have, in addition, pulmonary arteriovenous fistulas? Clagett et al.[12] have now partly answered this question. They studied 330 descendants of a young man who migrated from Germany to the United States in the '60s or '70s of last century, and who passed on the stigmata of hæmorrhagic telangiectasia to the generations that followed. It must be a close-knit family, for no fewer than 231 of them could be traced; and of this number 40% were found to have overt manifestations of the disease. When the investigation was narrowed down in a search for pulmonary arteriovenous fistulas, these were found to be present in 14 (i.e., 6·1% of the family group studied). In 8 it was found in a routine X-ray; in 6 there were symptoms and signs attributable to the bypass.

The finding of fistulas in such a high proportion of cases suggests that we should review from time to time all adult patients with hæmorrhagic telangiectasia; for the hazards of an uncorrected fistula can be formidable, including hæmothorax, thrombosis, and cerebral abscess. Whether we stumble on this lesion or unearth it only after diligent inquiry, its operative correction in every case may not be justified. The fistulas are often multiple, and it is important not to destroy too much healthy lung tissue. The need for operation will be determined by the number of fistulas and by their size and location.

BLOOD SAMPLES

BLOOD taken for the Wassermann reaction has proved useful for purposes besides the diagnosis of syphilis. Quite frequently a pathologist who has wished to establish normal values for some biochemical estimation, or to look for antibodies to some infection in the general population, has found his evidence in the sera left over from the W.R. Similar use has been made of blood taken for grouping or for biochemical tests. Such specimens have yielded some useful information but are far from perfect. In this country at any rate, those suspected of having syphilis are not a fair sample of the population; and those whose blood is sent to the biochemist will presumably be ill. Blood donors will be healthy, but there will be no children in the sample and the Registrar General's classes I and II will be over-represented. To obtain a random sample fortuitously is, in fact, almost impossible. Another difficulty with samples obtained by chance is the absence of useful information to accompany them: the discovery of brucella antibodies is almost meaningless without knowledge of the residence and occupation of the subjects.

As an improvement on the use of surplus blood specimens there is a lot to be said for the deliberate survey. The subjects can be chosen and classified on the spot. The serologist or biochemist (but rarely the hæmatologist) can collect his specimens in remote and barbarous places and examine them at leisure in a well-equipped laboratory. Such surveys have already given useful results on many subjects—for instance, the distribution of antibodies to poliomyelitis and the frequency of leptospiral infections in dogs. A publication from W.H.O.[1] contains some excellent advice and suggestions.

The simplest example is the establishment of a "normal" value in a static community; but the experimenter will soon find that, though the "normal" is a common animal, it is very hard to catch. Medical students and nurses are traditional normals but they represent limited age and social groups and are (or should be) the thing most hateful to the statistician—volunteers. The inmates of mental hospitals and gaols are less representative of the community as a whole than might be imagined. The most satisfactory sample among young adults is probably obtained from conscripted recruits to the armed services. It seems that less sophisticated communities are sometimes easier to sample. One of the most profitable uses of the survey method has been in the detection of influenzal antibodies in isolated villages. To judge from the published accounts the Eskimo in Greenland is far more generous with his blood than the English rustic. The success of the detailed surveys by the M.R.C. Pneumoconiosis Unit in the Rhondda Fach and elsewhere shows what sincerity and enthusiasm can do, but to obtain quite a small blood sample from a cross-section of the whole population of, say, Bournemouth would be difficult and time-consuming. Electoral rolls, school registers, and registrations of births allow the investigator to select a random sample within a limited age-group with precision, though he is likely to lose up to 20% owing to natural movements of the population. Persuading the subjects (and their mothers) to allow venepuncture is another matter: at no age is it painless or without risk of minor damage. The appeal for the general good which goes for little in the population as a whole can be a powerful weapon in a group of skilled tradesmen or an army unit. Persuasion gets a little attention in this booklet. It is a subject on which the serologist might be wise to consult the psychologist.

Samples of serum can be kept for years by freezing, and W.H.O. envisages a serum bank for use by investigators in the future. The idea is attractive and has already been put into action in a small way here and in the U.S.A., but we fear that its application may lead to some disappointments. Asking the right question at the right time is difficult enough, but to ask the questions which will be right in ten years' time will be a near-miracle. Multipurpose blood surveys are more promising, but without doubt those which have been most productive in the past have been those with limited objectives—e.g., the search for yellow-fever antibodies in Central Africa. But such surveys are neither cheap nor easy and they cause bother and discomfort to many; and anyone who undertakes them should have a clear conscience that what he does is for the general weal.

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Special Articles

INTERPRETATION OF CHROMOSOME COUNTS MADE ON BONE-MARROW CELLS

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IN a number of recent reports the distribution of marrow chromosome counts have been recorded from both normal and abnormal individuals.

The technique of making the bone-marrow preparations has been described by Ford, Jacobs, and Lajtha (1958), the basic steps being the short-term culture of the marrow cells in the presence of colchicine, the treatment of the cells with a hypotonic solution, and their subsequent squashing under a coverslip. The chromosomes are then counted in suitable cells—i.e., cells in which the chromosomes are well spread and lie as far as possible in the same optical plane. It is unusual, however, for every metaphase cell selected for counting to show the same number of chromosomes, and a range of chromosome counts is recorded in which the majority of atypical cells have a chromosome number less than the modal number.

In selecting cells for counting, cells considered unsuitable are those in which the chromosomes are poorly spread, those in which it is obvious that the cell has been ruptured and chromosomes lost, and those in which the appearances of the chromosomes indicate that one or more have been split at their centromeres into their sister chromatids. It is possible to ensure that in selected cells there are no chromosomes that have been obviously split at their centromeres; but it is not possible, in selecting cells for counting, to be certain that one or two of the chromosomes have not been lost.

In preparations made from bone-marrow in which there are no malignant cells it is customary to accept the modal number as the true somatic number of the individual and to regard counts differing from this as due to the presence of artefacts. It is possible, however, that in a normal bone-marrow there may be occasional cells with a true chromosome number different from the modal number, and it is also possible that an occasional individual may be a mosaic—i.e., his body may contain two or more stem lines with different chromosome numbers. Several such presumed mosaics have been reported by Ford and his coworkers (Ford et al. 1959, Ford 1959a), —i.e., an XX XXY mosaic containing cells with 46 and 47 chromosomes, and three XO XX mosaics with cells having 45 and 46 chromosomes.

Our object here is to discuss (1) the meaning of the variability of chromosome counts, and (2) the conditions to be fulfilled before a presumed mosaic can be accepted as a reality. Our assessment can be no more than preliminary, since the techniques are new and the preparative standards have changed appreciably over a short period; but a review seems desirable because the significance of the reported variations in chromosome number has been misunderstood.

For example, Ford, Jacobs, and Lajtha (1958) recorded a case of pernicious anæmia in which 25 out of 70 cells examined showed chromosome counts less than the modal number of 46, and it has been inferred from this by others that true numerical chromosome abnormalities may occur in the bone-marrow of patients with pernicious anæmia (*Lancet* 1959). Subsequently Ford (1959b) pointed out that this particular marrow preparation was made at a comparatively early stage in the development of the technique, and that the variation in chromosome number was most likely to have been due to preparative faults. The data from five untreated cases of megaloblastic anæmia which we give below support his conclusion, and on present evidence there appears no reason to doubt that such patients have a normal diploid number of 46.

Material

The marrow chromosome counts have been analysed from fifty-seven patients and ten healthy subjects in whom the modal number was 46, four with a modal number of 45, and thirteen with a modal number of 47. The materal was obtained from the following groups:

Modal Number: 46

A. Ten healthy males and females. Several of these were studied because their children had shown chromosomal abnormalities.

B. Four patients with testicular feminisation. Data for these have been published by Jacobs et al. (1959a).

C. Fourteen patients with ankylosing spondylitis.

D. Six patients with testicular cancer, in none of whom was there any evidence of metastatic spread.

E. Seven patients with male gonadal dysgenesis in whom the nuclear sex was male.

F. Five patients with primary amenorrhœa.

G. Five patients with untreated megaloblastic anæmia.

H. Nine patients with various congenital or genetically determined conditions.

I. Seven patients with various other conditions.

Modal Number: 45

J. Four patients with Turner's syndrome—i.e., female gonadal dysgenesis with a male nuclear sex and a chromosomal sex of XO. The data for one of these (H188) have been published by Jacobs and Keay (1959).

Modal Number: 47

K. Nine patients with mongolism, the data for four of whom (H114, H120, H122, H125) have been published by Jacobs et al. (1959b).

L. Three patients with Klinefelter's syndrome—i.e., male gonadal dysgenesis with a female nuclear sex and a chromosomal sex of XXY. The data for one of these (H54) have been published by Jacobs and Strong (1959).

M. One patient with a female nuclear sex and a chromosomal sex of XXX—the " super-female " described by Jacobs et al. (1959c).

It will be noted that in the descriptions of the eleven cases which have been published previously, the chromosome counts relate in each instance to a larger number of dividing cells than those given in the present tables. The reason is that our practice has been to score the counted cells in two ways, distinguishing the results for those cells for which there have been no doubt about the counts from those cells for which the exact number of chromosomes is uncertain. In these latter a decision was made as to which category of chromosome number each cell was most likely to belong to, and, in the previously reported counts, both the certain and the uncertain cells have been included. In this and subsequent communications unless otherwise stated, we shall report cells only when an exact count can be made.

Results

The data for patients with a normal chromosome number are given in table 1; the numbers of cells which contained less than 44, 44, 45, 46, 47, 48, and more than 48 chromosomes are shown separately. Polyploid cells were seen in many of the preparations, but these cells have been excluded because the standards required to recognise a polyploid cell are less strict than those required to determine the exact number of chromosomes in a diploid cell. The proportion of polyploid cells recorded in a

count is therefore likely to be misleading, unless it is sought as a separate item.

The total number of cells in each category has been summed for each group of conditions in table I; and the grand totals have been determined for sixty-seven subjects. Altogether 1602 cells have been counted; of these 1362

TABLE I—CHROMOSOME COUNTS IN SIXTY-SEVEN PERSONS WITH A MODAL NUMBER OF 46

Group	Patient	Diagnosis	<44	44	45	46	47	48	>48	Total	Probability‡
A	H 79	Normal male	..	2	3	24	..	..	1	30	0·221
	H110	,, ,,	..	2	2	20	..	..	..	24	0·391
	H172	,, ,,	2	..	2	9	..	..	..	13	0·062
	H 83	,, female	..	1	2	31	1	..	..	35	0·705
	H106	,, ,,	..	..	2	21	..	..	..	23	0·786
	H111	,, ,,	1	..	1	16	1	..	..	19	0·438
	H112	,, ,,	2	2	1	43	..	..	..	48	0·806
	H129	,, ,,	..	1	1	16	..	..	..	18	0·648
	H159	,, ,,	1	3	..	22	1	..	..	27	0·487
	H173	,, ,,	..	..	..	10	..	..	..	10	0·902
Totals			6	11	14	212	3	..	1	247	..
B	H113	Testicular feminisation	1	1	3	25	1	..	..	31	0·245
	H139	,, ,,	1	1	2	25	..	..	..	29	0·548
	H141	,, ,,	..	..	2	9	..	..	..	11	0·364
	H149	,, ,,	..	..	2	21	..	..	..	23	0·786
Totals			2	2	9	80	1	..	..	94	..
C	H 1	Ankylosing spondylitis	2	1	1	16	1	..	..	21	0·140
	H 33	,, ,,	..	..	..	8	1	..	..	9	0·584
	H 42	,, ,,	..	..	2	5	1	..	..	8	0·063
	H 48	,, ,,	..	2	2	26	1	..	..	31	0·412
	H 49	,, ,,	..	1	..	21	..	..	..	22	0·918
	H 58	,, ,,	..	1	2	23	2	..	..	28	0·324
	H 72	,, ,,	2	..	1	20	2	1	..	26	0·134
	H193	,, ,,	..	..	3	18	5	..	..	26	0·022
	H197	,, ,,	1	1	1	11	..	..	..	14	0·249
	H201	,, ,,	..	..	1	12	..	..	..	13	0·740
	H203	,, ,,	..	..	1	15	..	..	..	16	0·821
	H206	,, ,,	..	..	1	11	..	..	..	12	0·707
	H212	,, ,,	..	1	1	27	1	..	..	30	0·764
	H216	,, ,,	..	..	..	27	..	..	..	27	0·994
Totals			5	7	16	240	14	1	..	283	..
D	H 2	Carcinoma testis	1	..	6	28	1	1	..	37	0·067
	H 52	,, ,,	1	..	1	6	..	..	..	8	0·224
	H 55	,, ,,	1	..	2	25	1	..	..	29	0·548
	H202	,, ,,	..	..	1	6	..	..	..	7	0·481
	H208	,, ,,	..	..	..	19	1	..	..	20	0·892
	H222	,, ,,	..	..	2	21	1	..	..	24	0·608
Totals			3	..	12	105	4	1	..	125	..
E	H 62	Male gonadal dysgenesis (−ve)*	..	..	3	9	1	..	..	13	0·062
	H 78	,, ,, ,, ,,	..	..	3	13	1	..	..	17	0·172
	H 84	,, ,, ,, ,,	..	..	1	24	..	..	..	25	0·945
	H 92	,, ,, ,, ,,	..	2	2	69	..	..	..	73	0·993
	H109	,, ,, ,, ,,	..	..	2	19	..	..	..	21	0·738
	H117	,, ,, ,, ,,	1	..	1	23	1	..	..	26	0·666
	H195	,, ,, ,, ,,	..	..	1	14	..	..	..	15	0·797
Totals			1	2	13	171	3	..	..	190	..
F	H126	Primary amenorrhœa	..	..	2	26	..	..	..	28	0·875
	H167	,, ,,	..	1	2	5	..	..	..	8	0·062
	H170	,, ,,	..	..	2	10	1	..	..	13	0·184
	H191	,, ,,	..	..	1	9	..	..	..	10	0·629
	H194	,, ,,	..	..	2	14	2	..	..	18	0·200
Totals			..	1	9	64	3	..	..	77	..
G	H 81	Megaloblastic anæmia (untreated)	2	1	6	66	2	..	..	77	0·554
	H 95	,, ,, ,,	..	..	1	25	2	..	..	28	0·717
	H136	,, ,, ,,	..	..	2	21	..	..	..	23	0·726
	H204	,, ,, ,,	..	..	1	17	..	..	..	18	0·861
	H223	,, ,, ,,	1	1	..	12	1	..	..	15	0·288
Totals			3	2	10	141	5	..	..	161	..
H	H130	Achondroplasia	1	1	2	13	..	..	..	17	0·172
	H132	,,	..	2	2	52	..	..	..	56	0·956
	H134	Epiloia	..	1	3	22	1	..	..	27	0·294
	H135	Microcephaly	..	1	1	14	..	..	..	16	0·578
	H161	?†	..	1	3	22	1	..	..	27	0·294
	H164	Albright's disease	1	1	..	5	..	..	..	7	0·178
	H171	Female gonadal dysgenesis (+ve)	3	2	2	26	..	..	..	33	0·164
	H178	True hermaphroditism	1	1	..	6	..	..	..	8	0·224
	H220	? Juvenile amaurotic idiocy	2	1	5	27	1	..	..	36	0·058
Totals			8	11	18	187	3	..	..	227	..
I	H 47	Pulmonary tuberculosis	..	..	..	17	..	..	..	17	0·968
	H 60	Adrenal virilism	1	1	4	24	..	..	..	30	0·221
	H 75	Megaloblastic anæmia (treated)	..	..	5	24	2	..	..	31	0·245
	H 89	,, ,, (,,)	1	..	1	41	..	..	..	43	0·979
	H115	Hæmolytic anæmia	2	1	5	18	3	..	..	29	0·001
	H155	Infectious mononucleosis	3	..	3	19	2	..	..	27	0·027
	H207	,, ,,	..	1	1	19	..	..	..	21	0·738
Totals			7	3	19	162	7	..	..	198	..
All		All patients	35	39	120	1362	43	2	1	1602	..
		Percent	2·19	2·43	7·49	85·02	2·68	0·13	0·07	100·00	..

*(− ve) and (+ ve) indicates male and female nuclear sex.
†H161. This patient presented with short stature, webbing of neck, unusual thickening of the occiput, a high arched palate, myopia, and strabismus. He was originally thought to be perhaps a male example of Turner's syndrome.
‡ See footnote (p. 162).

TABLE II—PROBABILITY OF OBTAINING THE OBSERVED PROPORTIONS OF TYPICAL AND ATYPICAL CELLS IN NINE GROUPS OF PATIENTS WITH NORMAL KARYOTYPES

Group (no. of subjects)	Value of χ^2	Probability (n=1)
A. Healthy men and women (10)	0·150	Between 0·1 and 0·9
B. Testicular feminisation (4)	0·001	0·97
C. Ankylosing spondylitis (14)	0·012	0·91
D. Testicular cancer (6)	0·110	Between 0·1 and 0·9
E. Chromatin-negative male gonadal dysgenesis (7)	4·200	0·04
F. Primary amenorrhœa (5)	0·230	Between 0·1 and 0·9
G. Untreated megaloblastic anæmia (5)	0·920	,, ,,
H. Various congenital or genetically determined conditions (9)	1·447	,, ,,
I. Various other conditions (7)	1·817	,, ,,

(85·0%) contained 46 chromosomes. Examination of the distribution of cell counts shows that the distribution is not symmetrical but is negatively skewed, and that 12·1% of cells give counts of less than 46 in contrast to 2·9% with counts in excess of 46. This greater preponderance of "atypical" cells with counts of less than 46 chromosomes is seen in all the groups and, in each of them, the most common type is a cell with a count of 45 chromosomes.

The homogeneity of the material shown in table I may be tested by comparing separately the data for each group of patients with those obtained from all the groups together. The results (table II) show that the variation in the proportion of atypical cells in each group can reasonably be attributed to chance. The most extreme variation (group E) would be expected to occur once in 25 tests. This figure must be interpreted in the light of the fact that nine groups were examined and it is reasonable to suppose that among so many groups a probability of this order would occur at least once due to chance factors alone (P=0·44).

A more detailed analysis has also been made by examining for each patient the probability of obtaining the observed proportion of cells with modal and non-modal counts. These have been obtained from published Binomial Tables by assuming that the expected proportion of cells with non-modal counts was 15%.* The distribution of the individual probabilities is shown in table III. From the table it appears that there is a tendency to record counts with the more extreme probabilities; but, with the present number of observations, we cannot be sure that this is not a chance finding ($\chi^2=11·66$, n=9, $0·2<P<0·3$). The most extreme probability recorded was in case H115 (a man with idiopathic acquired hæmolytic anæmia); in this subject 8 of 29 cells counted showed 45 or less chromosomes and 3 cells showed 47 chromosomes. The probability of recording so many or more atypical cells is estimated at about 0·001. In our series of sixty-seven patients one probability of this order can be expected, by mere chance, slightly more often than once in 20 times (P=0·06). It may be noted, however, that in this extreme case, the marrow preparation was regarded as technically poor before the count was made, and the whole preparation may well have contained more than the usual proportion of artefacts.

TABLE IV—CHROMOSOME COUNTS IN FOUR PERSONS WITH A MODAL NUMBER OF 45

Patient no.	Diagnosis	<43	43	44	45	46	47	>47	Total	Probability
H 98	Turner's syndrome	4	9	9	57	..	..	..	79	0·002
H138	,,	1	1	..	38	..	1	..	41	0·919
H153	,,	2	..	..	6	1	..	..	9	0·087
H188	,,	..	..	1	19	..	..	..	20	0·893
Total		7	10	10	120	1	1	..	149	..

Difference between proportions of atypical cells, patients with modal number of (*a*) 46 and (*b*) 45:
$\chi^2=2·105$, n=1, $0·1<P<0·2$

* Since it was desired to examine the distribution of probabilities, the figure given is the probability of obtaining more than the observed number of non-modal cells plus half the probability of obtaining the number actually observed. This overcomes the difficulty resulting from the fact that the variable concerned is discontinuous. The mathematical justification for this technique is discussed by Lancaster (1949).

TABLE V—CHROMOSOME COUNTS IN THIRTEEN PERSONS WITH A MODAL NUMBER OF 47

Group	Patient no.	Diagnosis	<45	45	46	47	48	49	>49	Total	Probability
J	H114	Mongolism	1	..	2	35	3	1	..	42	0·367
	H119	,,	..	..	..	5	..	..	..	5	0·778
	H120	,,	..	1	4	22	..	..	..	27	0·295
	H121	,,	1	..	2	10	..	1	..	14	0·097
	H122	,,	..	1	2	33	1	..	..	37	0·748
	H124	,,	..	..	1	5	..	..	..	6	0·423
	H125	,,	..	1	1	31	..	2	..	35	0·705
	H127	,,	1	2	2	5	1	..	..	11	0·001
	H205	,,	2	..	..	16	..	..	..	18	0·648
Total			5	5	14	162	5	4	..	195	..
K	H 54	Klinefelter's syndrome	..	1	5	20	2	1	..	29	0·141
	H100	,,	1	5	5	62	4	..	..	77	0·030
	H151	,,	..	1	1	12	..	..	..	14	0·498
Total			1	7	11	94	6	1	..	120	..
L	H152	"Super-female"	1	1	4	49	..	..	..	55	0·795
Total all groups			7	13	29	305	11	5	..	370	..

Difference between proportions of atypical cells, patients with modal number of (*a*) 46 and (*b*) 47:
$\chi^2=1·538$, n=1, $0·2<P<0·3$

The data for patients whose cells show abnormal numbers of chromosomes are summarised in table IV (modal number 45) and in table V (modal number 47). In both the proportion of atypical cells is slightly greater than that recorded for subjects with a normal modal number of 46—i.e., 19·5% and 17·6% atypical counts compared with 15·0%. In neither is the difference significant; but the number of patients examined is still small and, if the expected proportion of non-modal counts was 15%, there were two patients (H 98 with Turner's syndrome, and H 127 with mongolism) with a type of count which would be expected to occur less often than once in 100 times. On the basis of these data, it seems wise to suspend judgment about whether the cells of patients with an abnormal karyotype may also show abnormal variability in the number of their chromosomes.

Discussion

In reporting the distribution of chromosome counts it has generally been accepted that the modal number represents the true somatic number, and that deviations from it are due to preparative faults. One may reasonably suppose, however, that mitotic errors occasionally occur in somatic tissues and give rise to cells with chromo-

TABLE III—PROBABILITY OF OBTAINING THE OBSERVED PROPORTION OF TYPICAL AND ATYPICAL CELLS: COMPARISON OF OBSERVED AND EXPECTED DISTRIBUTION (67 SUBJECTS WITH NORMAL KARYOTYPE)

No. of subjects	Probability										All probabilities
	<0·100	0·100–0·199	0·200–0·299	0·300–0·399	0·400–0·499	0·500–0·599	0·600–0·699	0·700–0·799	0·800–0·899	0·900 or more	
Observed	9	7	11	3	4	5	4	11	5	8	67
Expected	6·7	6·7	6·7	6·7	6·7	6·7	6·7	6·7	6·7	6·7	67

some numbers different from the modal number. These errors are presumably due to non-disjunction, and are comparable to those that occur during parental gametogenesis. In the latter case the affected gametes give rise to monosomic or trisomic individuals, so far represented in man by the clinical conditions of Turner's syndrome, Klinefelter's syndrome, mongolism, and the "superfemale". Ford and his colleagues have advanced the general argument that if a non-disjunctional error causes the loss of the Y chromosome in some of the cells of an XXY zygote, producing normal XX cells, and if normality offers some selective advantage over the cells with the abnormal trisomic condition, then a mosaic state could arise. Mosaicism could also be the result of a non-disjunctional error at an early stage in the development of a normally constituted zygote, one of the resultant abnormal cells dying and the other persisting to give rise to a clone of cells with an abnormal chromosome number.

There are, therefore, three possible reasons for the observed variation in marrow chromosome counts: (1) artefacts, (2) mitotic abnormalities, and (3) mosaicism.

In performing chromosome counts particular attention is paid to the cells in which the count differs from the modal number. In our opinion the great majority of such cells arise during preparation, the most common fault being the rupture of the cell with the loss of one or more chromosomes. Detailed study of the cells containing one chromosome more than the modal number reveals no evidence of an artefact, but there are reasons for thinking that the count is genuine in only a minority. In the others the atypical count is due either to unrecognised splitting at the centromeres (the sister-chromatids being widely separated and enumerated as two chromosomes) or to the inclusion of a chromosome from a neighbouring cell. If some of the cells with excess chromosomes are genuine there are also likely to be a few cells with true counts less than the modal number, though these cannot be distinguished from cells which have lost a chromosome or chromosomes through cell rupture. The data from individuals with a normal karyotype (table I) show that less than 3% of cells have counts above the modal number. Even if all these represented genuine aberrations from the modal number (which is very unlikely) and there was an equal proportion of cells with a true count less than the modal number, it would still follow that the majority of atypical cells were artefacts.

In view of the variability of the counts in normal individuals it is clearly difficult to prove that a particular count indicates a mosaic. In our opinion three criteria need to be fulfilled before the diagnosis can be established.

1. The number of cells with counts different from the modal number must be more than can reasonably be attributed to chance. (As more subjects are examined, more extreme variations are certain to be observed due to chance alone.)

2. The excess of atypical cells must be demonstrable in two or more separate bone-marrow examinations and preferably in two or more tissues. A suitable technique has been evolved for the study of chromosomes in the culture of skin (Harnden 1959); but a negative result from skin culture may not contradict the findings from marrow cultures, as two cell lines may be freely mixed within the marrow but occupy topologically distinct areas of skin, or mosaicism may be confined to the bone-marrow and not involve other tissues.

3. A detailed analysis of the chromosomes in cells containing more or less chromosomes than the modal number must provide evidence that a high proportion of such cells have the same karyotype—i.e., that the additional or the missing chromosomes are the same ones in different cells.

The proportion of atypical cells reported by Ford and his coworkers in four patients (one presumptive XX/XXY mosaic, and three presumptive XO/XX mosaics) is much higher than could reasonably be attributed to chance on the basis of our experience. It is, however, unsatisfactory to use data compiled by one group to test the significance of data collected by others and, so far as our own data are concerned, there is no reason to postulate the occurrence of a mosaic among the first eighty-four subjects to be examined.

Summary

The distribution of chromosome counts has been analysed from the bone-marrow preparations of sixty-seven people who have shown an apparently normal karytope.

The distribution is negatively skewed around the modal number of 46, 85% of the cells showing a count of 46 and approximately 12% a count less than 46. Of the latter more than half showed a count of 45 chromosomes. The reasons for this type of distribution are discussed.

The chromosome counts in four people with a modal number of 45 and in thirteen with a modal number of 47 have also been studied. While the number of such persons is small the indications are that no unusual distribution of counts occurs, although more data are required for a final conclusion.

Certain criteria are suggested, which ought to be satisfied before a diagnosis of a chromosomal mosaic involving two or more cell lines can be substantiated.

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CASUALTIES AND CASUALS

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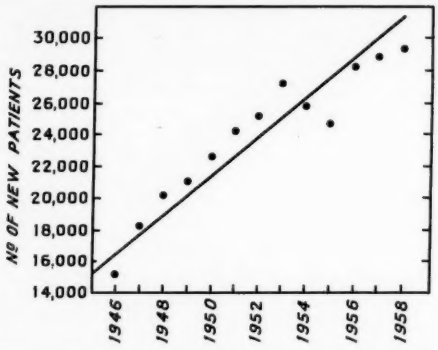
THOUGH within the bounds of the hospital, the casualty department is an entity of its own, usually staffed by junior doctors with a very brief term of service. Papers have been written and suggestions made on how it should be planned (Clarkson 1956, Lowden 1956, Bowen 1957, Hilzinger and McAllister 1957, Shortcliffe 1958) but little is known about the character, incidence, and disposal of the cases seen in it. The only previous analysis known to me was confined to medical patients (Mestitz 1957).

I record here my experience of 5000 attendances seen by me consecutively in the casualty department of a London teaching hospital, between July and December, 1958.

The Department

The hospital is in south-east London, in a densely populated area. Most of the people belong to the lower social classes, and there are about 25,000 Jamaicans in the neighbourhood.

The department has a medical staff of five. Two are post-registration appointments, and three are pre-regis-



Increase of new patients attending casualty department.

tration. Two of the pre-registration housemen work also in other departments of the hospital. The casualty officers are ultimately responsible to a consultant surgeon at the hospital.

Patients can be admitted under the casualty officer for up to forty-eight hours (after which they must be referred to the appropriate department), or they can be referred direct to a consultant. Referral from casualty to the outpatient department is by the usual method. All fractures are seen next day in the casualty fracture clinic, which is the responsibility of the orthopædic department.

The continuing increase in the number of new patients is shown in the figure.

Reattendances in the department (at the doctor's request) tend to rise when a new set of casualty officers take up their posts, or when locums are employed. Requests for reattendance also vary with the individual doctor. In my personal series there were 2935 new patients (60%) and 2065 reattendances (40%).

The Series

The age-distribution of the 5000 patients is shown in table I.

TABLE I—AGE-DISTRIBUTION

0–9	10–19	20–29	30–39	40–49	50–59	60–69	70+
799	1060	985	765	641	342	178	230
16%	21%	20%	15%	13%	7%	3·5%	4·5%

There was a male preponderance of 3 to 1 (3680 males and 1320 females).

The sources of the new patients were:

Casuals (patient comes on own initiative)	1825 (62·5%)
Referred by general practitioner	711 (24%)
Accidents	303 (10%)
Other emergencies	96 (3·5%)
Total	2935 (100%)

Thus nearly two-thirds of the new patients were "casuals", many of whom could have been dealt with by the family doctor. Mestitz (1957) in his series found that 80% of the medical patients in the casualty department were casuals.

A third (980) of the new patients were X-rayed, and 8% (170) had investigations (other than urine testing) on attending the department. The majority of these were culture of pus from septic lesions.

The diagnoses are shown in table II.

The cases of *trauma* (51%) may be subdivided as follows:

Minor trauma	1042 (71%)
Major trauma	22 (1·5%)
Fractures	272 (18%)
Head injuries	94 (6%)
Burns	56 (3·5%)
Total	1486 (100%)

Of the 286 cases of *sepsis* 119 (41%) required surgery.

Of the 284 cases classified as *surgical*, 36 (12%) were acute—e.g., acute abdomen. Of the remaining 248—e.g., orthopædic problems, patients with pain in the abdomen, or various swellings, sent to casualty for an opinion—only 57 (23%) required minor surgical procedures in the department.

Of the 338 *medical* cases, 78 (23%) were regarded as acute—e.g., overdose of barbiturates, coal-gas poisoning, cardiac infarction, hæmatemesis, epilepsy, or cerebrovascular accident. Another 50 (15%) had obviously psychiatric illness (not the minor neurosis from which a number of the patients were probably suffering).

The remaining 210 (62%), classified as non-acute, comprised a very wide range of conditions met with in everyday general practice, varying from peptic ulcer and longstanding cardiac failure to constipation, infections of the upper respiratory tract, and the exanthemata.

Of the 115 *ophthalmic* cases, 90 (78%) were grouped as minor trauma and foreign bodies, while the other 25 (22%) were not casualty problems but outpatient problems.

E.N.T.—Of the 87 *ear, nose, and throat* cases, 68 (78%) were "medical" (the type of case common in general practice): these included tonsillitis, acute otitis media, and acute sinusitis. The rest were "surgical"—i.e., fishbones in the throat, foreign bodies in the ears or nose, or epistaxis.

TABLE II—DIAGNOSTIC CLASSIFICATION

Trauma	Sepsis	Surgical	Medical	Eyes	E.N.T.	Miscellaneous	Total
1486	286	284	338	115	87	339	2935
51%	10%	10%	11%	4%	3%	11%	100%

E.N.T. = ear, nose, throat.

Finally, the *miscellaneous* group of 339 patients included 152 dental cases (5% of the total new attendances), 10 obstetric and gynæcological cases, 48 drunks, 8 cases certified dead on arrival, and 74 in which nothing abnormal could be found. This leaves 47 unclassified, such as the woman who wanted her coffee analysed for an aphrodisiac, and a number of overseas visitors who had run out of their tablets, &c., while on holiday in England.

Table III relates the main diagnostic groups (table II) to the source of the patient.

A comparison of casuals with cases referred by practitioners shows considerable similarity. In both groups half the cases were trauma, and about 10% were sepsis. In the surgical group, however, there is a higher proportion of cases referred by practitioners. Patients were often sent to the casualty officer for a second opinion (in many cases it was a "pre-registration" opinion), for minor surgical procedures, or as a bypass to the outpatient department. Under the heading of "medical", the casuals have a much higher proportion of psychiatric cases than the referred patients, but the latter are a selected group in that many were sent to the casualty department as a means of avoiding waiting-lists, or for a second opinion. That more of the "miscellaneous" group are casuals is due to the casuals including more dental cases.

TABLE III—DIAGNOSTIC GROUPS RELATED TO SOURCE OF PATIENTS (%)

—	Trauma	Sepsis	Surgical	Medical	Eyes	E.N.T.	Miscellaneous	Total
Casuals	50	10	8	10·5	6	3	12·5	100
Referred by general practitioner	48·5	12·5	19	10	1·5	2·5	6	100
Accidents	88	..	0·5	1	1	..	9·5	100
Emergencies	..	..	4	73	..	..	23	100
Total	51	10	10	11	4	3	11	100

TABLE IV—DISPOSAL OF NEW PATIENTS

—	Trauma	Sepsis	Surgical	Medical	Eyes	E.N.T.	Miscellaneous	Total
Reattend	500 (33%)	252 (88%)	91 (32%)	41 (12%)	76 (67%)	13 (15%)	7 (2%)	980 (33%)
Discharged	490 (33%)	10 (4%)	33 (12%)	95 (29%)	25 (21%)	28 (32%)	203 (60%)	884 (30%)
Referred to general practitioner	160 (11%)	23 (8%)	28 (10%)	55 (16%)	2 (2%)	33 (38%)	18 (6%)	319 (11%)
Admitted at once	128 (9%)	..	31 (11%)	77 (23%)	..	..	28 (8%)	264 (9%)
Referred to another department in the hospital	204 (14%)	..	98 (34%)	54 (15%)	12 (10%)	13 (15%)	61 (18%)	442 (15%)
Miscellaneous*	4	1	3 (1%)	16 (5%)	..	..	22 (6%)	46 (2%)
Total	1486 (100%)	286 (100%)	284 (100%)	338 (100%)	115 (100%)	87 (100%)	339 (100%)	2935 (100%)

*e.g., referred to duly authorised officer; self discharges.

Of the emergencies—i.e., those brought by ambulance—73% were medical, and of these nearly a quarter were classified as psychiatric. (This does not include the large proportion of attempted suicides which were classified as acute medical.) It is also noteworthy that 4 patients of the accident group were classified as psychiatric. They had attempted suicide by physical means but were found to have no physical injuries.

Table IV shows the disposal of the patients.

Of the casuals, about half were discharged from hospital treatment (table V); 15% were definitely hospital problems, being either admitted or referred to another department, and 35% were retained under the care of the casualty department. Of the patients referred by practitioners, 25% were sent back to their doctor, 25% had eventually to be referred to another hospital department,

TABLE V—DISPOSAL RELATED TO SOURCE OF PATIENTS (%)

—	Re-attend	Dis-charged	Re-ferred to G.P.	Re-ferred to other dept.	Ad-mitted	Miscel-laneous	Total
Casual	35	39·5	9	12·5	3	1	100
Referred by general practitioner	27·5	13	25	25	9	0·5	100
Accident	30	18·5	3	9	36·5	3	100
Emergency	1	33	5	7	41	13	100

and 9% required admission, although the casualty officer was not responsible for admitting practitioners' patients.

40% of the accidents and emergencies were admitted. On the other hand 17·5% of accidents and 33% of emergencies were discharged on their first visit, although all had arrived in ambulances. Mestitz (1957) thought that, of 52 medical patients reaching casualty by ambulance, only 29 needed such transport.

Table VI shows the average number of visits (first and subsequent combined) for each diagnostic group, and the number of reattendances for these groups.

Taken together, tables IV and VI show that trauma, sepsis, and eye cases accounted for 84·5% of the re-

TABLE VI—NUMBER OF VISITS OF REATTENDERS AND AVERAGE NUMBER OF VISITS FOR A PATIENT ATTENDING THE DEPARTMENT

—	No. of visits of reattenders	Average no. of visits per patient
Trauma	1015 (49%)	1·5
Sepsis	572 (28%)	3·7
Surgical	190 (9%)	1·6
Medical	110 (5%)	1·3
Eyes	151 (7·5%)	2·3
Ear, nose, throat	9 (0·5%)	1·1
Miscellaneous	18 (1%)	1·0
Total	2065 (100%)	1·8

attendances, though they formed only 65% of the new cases. These groups may be regarded as "specific" casualty problems. Patients with "sepsis" paid more visits to the department than any other group. The fact that the average number of attendances is 1·8 indicates that most patients are not retained under the department for any length of time.

There were two reasons for asking patients to come again. Firstly, treatment begun in the department and regarded as "casualty treatment" is continued there. The second reason was to check on a case. The casualty officer is acutely aware of litigation against his section of the medical profession, and most pre-registration housemen lack the confidence, or clinical judgment, needed to discharge some of the patients who do not require further hospital treatment. Reattendances in the department generally fall towards the end of the casualty officer's term of office, when he has acquired more confidence.

Discussion

The word "casualty" implies an accident or a serious or fatal event, but present-day casualty work is certainly not confined to accidents. Indeed it could literally be called "general practice", for every aspect of medicine is encountered. This conforms to the pattern before the National Health Service when patients attended the hospital outpatient or casualty department for all manner of illnesses because they could not afford the doctor's bills. With the advent of the N.H.S., casual attenders might have been expected to disappear from the hospital, but at King's College Hospital the number of new patients has nearly doubled in the past twelve years (see figure).

Present Status of Casualty Department

Agreement has not yet been reached on the part the casualty department should play. Should it see all patients who present themselves or should some selection be enforced? In my own series only 60% of cases were "casualty" problems, and of these the majority were minor trauma.

Nearly two-thirds of the attendances were by the casual attender. Reasons for such visits were:

1. Some patients had themselves decided that their problem was one for the hospital—either because they thought it urgent, or because they felt they needed special investigations or treatment.

2. A few patients said that their doctors "would only have sent them to hospital anyway, so they came themselves".

3. Some had tried to contact their doctor, but had failed.

4. The casualty department was always open, and this suited them better than their doctor's surgery hours. Also they thought they would have to wait less time in casualty than in their doctor's surgery. (In this they were sometimes mistaken.)

5. Some were not on any practitioner's list, or were staying only temporarily in the area and thought they could not call on a doctor.

6. A few were dissatisfied with their doctor and wanted a second opinion.

7. A proportion were sent from work or school.

Are these reasons adequate? I doubt if all of them are. In this country everybody is now entitled to a family doctor who should be responsible for his health and welfare. If both the hospital and the family doctor are available for the patient to choose between, the result is duplication of services and weakening of the doctor-patient relationship. Who should decide whether he goes to the casualty department—the patient himself or his doctor? When he is sure that he will be sent on to the casualty department, the patient naturally wants to avoid an unnecessary visit to his doctor first. But, apart from this, some people seem to prefer hospitals to general practitioners.

Use of Casualty by Family Doctor

General practitioners referred cases for various reasons:

1. Trauma, for an X-ray to exclude bony injury, for suture of lacerations, or for treatment of fractures. The X-ray department is not directly accessible to practitioners.

2. Septic cases and a proportion of the surgical cases are referred for minor surgery. Of the septic conditions referred, two-thirds eventually had surgical treatment.

3. Some patients were sent for a second opinion—either directly from the casualty officer or from the outpatient departments to which casualty gives indirect access.

4. Some cases were sent for admission without previous inquiry on whether the hospital had a bed for the patient.

5. In a small but significant number of cases the patient was sent for social reasons. An old lady of 94 arrived with the following note: "Will you please admit this patient. I can find nothing wrong with her except old age". And some acute "psychiatric" conditions were referred to the department, for "social" reasons.

Of these groups the true "casualty" problems were the trauma patients for minor surgery and a small proportion of the cases sent for admission—e.g., overdose of drugs. These amounted to about 60% of the referred cases. The other 40% were a misuse of the casualty department, for they could have been dealt with through other channels.

Future of the Casualty Department

Function.—To have duplication of medical services is both uneconomical and unnecessary. Casualty, like any other service, should have a specific function, and in my view it should deal only with trauma, emergencies (acute medical or surgical cases, 2% in this series), and minor surgery.

Design.—Dependent upon function, the department should be composed of three units—one for trauma, one for minor surgery, and one for emergencies. The trauma unit should have its own beds, and be responsible for inpatient and outpatient care in its specialty.

Staffing.—The casualty department should be under senior hospital medical staff, who would be responsible for supervising and training the junior casualty officer.

Centralisation.—Obviously such a casualty department would not be needed in every hospital. A given area should have its casualty centre at one particular hospital, where it would be maintained and staffed for its special purpose. Centres should be fewer but better: at present many of the casualty departments in this country are staffed by the pre-registration house-physician or house-surgeon on duty—people with no casualty experience.

The future casualty department should not cater for the casual attender. He has his family doctor to consult if he needs medical advice.

Summary

This paper analyses 5000 attendances at a south-east London casualty department. The patients form a consecutuve series seen by one casualty officer.

2935 (60%) were new attendances, and nearly two-thirds of these were casual attenders not referred by a doctor. Only half the new patients were classified as trauma.

In this department the number of new patients has doubled over the past twelve years, though under the National Health Service all patients can go to their family doctor without expense.

The present-day casualty department has no specific function and runs as a "general practice". It is misused to a considerable extent both by the public and by their doctors.

Future casualty departments should have a specific role. Meanwhile more work is necessary both to review existing casualty services and to define their proper function and location.

I should like to thank Mr. L. T. Cotton for permission to conduct this survey, and the casualty reception staff for their valuable cooperation. My thanks are also due to Dr. John Fry for his encouragement and criticism. But the views I express are my own.

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DOCTORS AND NATIONAL SERVICE

THE chairmen of the National Medical Manpower Committee and of the Central Medical Recruitment Committees have issued the following statement:

"The announcement made by the Minister of Labour on Dec. 14, 1959, that certain persons whose deferment for training or study ends on or after June 1, 1960, will not be called up does not apply to doctors or dentists. Doctors liable for National Service have always been dealt with under special and separate arrangements through the three professional committees, which advise on deferments and call-up matters. These special arrangements will continue until the end of 1960, when call-up is planned to end.

"Under these arrangements deferment granted for completion of studies is continued during the pre-registration year, during which all doctors receive a memorandum setting out the arrangements for call-up and for further deferment.

"Doctors who become provisionally registered as medical practitioners on or after Jan. 1, 1960, and doctors granted deferment of call-up to a date beyond the end of 1960 need not, subject to fulfilment of their deferment conditions, expect to be called up except in emergency.

"All other doctors will, if fit, be considered for call-up in the usual way. They will accordingly be nominated for National Service commissions (two years), unless they volunteer to enter the Forces on short service or regular commissions, or unless their call-up is deferred by the Central Medical Recruitment Committees on professional grounds or postponed by the Ministry of Labour on grounds of exceptional hardship.

"In 1960 the Forces will still have substantial requirements for medical officers, which will need to be met largely from doctors liable for National Service. This means that a considerable number of such doctors must expect to be called up during 1960."

In England Now

A Running Commentary by Peripatetic Correspondents

READERS of the best spy stories have long realised that to qualify for the higher echelons of spying a man must be a polished cracksman, a fluent polyglot, and a perfect shot (knife and gun); he must know the odds and modes of cheating at all games of skill and chance; and (if he is a hero) he must also be an appreciative connoisseur of life, for otherwise the Game would hardly be worth the candle—especially as the candle is usually alight at both ends and will be applied to the soles of his feet sooner or later. Of course, if he is a villain, villainy alone is a sufficient motive.

In view of all this literary conditioning, it is doubtful whether there are many people in England who really believe that spies exist. Ours is a land of charming naïveté where evil is concerned—a land of amateurs. We are not accustomed to consider blackmail, perversion, and revenge as common reasons for adopting a profession so inconvenient as intrigue appears to be. We have built up a melodramatic picture of the spy; and, because in our watercolour country we have come to regard as mildly absurd whatever is vivid, we find the idea of the sinister spy either ridiculous or incredible. Probably we shall never be able to assess the evidence on which the accusation was made that a Communist diplomat set afoot the grotesque plan to poison most of the staff of Radio Free Europe by putting atropine in the saltcellars of the canteen. The idea is too fantastic; the English imagination boggles—and then is tempted into a shamefaced chuckle at the notion of several hundred people simultaneously stuffing themselves with deadly nightshade. As like as not, tasteless jokes about the tastelessness of institutional soup will soon become current in student circles, while dons will quote the *Mithridates* passage from Housman or exchange thin-lipped smiles when the cruet passes between the protagonists of some High Table feud.

With our flippant heritage, how can we fail to look on the Bad Man as an object of pity and of decently moderate derision? Anarchists, nihilists, world-dominators, men who hate women, women who hate men, Nazi fascists, inquisitors, Communist fanatics—we are sorry for them. Why do these people make themselves so wretched, we ask first; and then—why must they also try to make *us* wretched? Can it be that for them happiness is harder work than spying, cheating, lying, destroying, torturing? And if this is true for certain individuals, can it also be true for whole nations? And is extremism always destructive; or is there a cause into which it is right to throw all our energies without reservation? Only one suggests itself: the cause of sanity—in other words, of realism, compassion, humour, and truth. These are virtues which never start wars, although, if necessary, they will *wage* war, invincibly.

* * *

Little attention is usually paid to hospital fauna, but ours at least are interesting.

A pet tortoise survived the whole of the war and on its demise was buried outside the operating block. Its tombstone was inscribed with the touching lines:

> " Chloe was a beautiful tortoise,
> Even in rigor mortis "

The other day I went into one of the anæsthetic rooms and found a robin perched on a gallipot pecking away at some K-Y jelly which was used to lubricate airways. As I believe that this substance contains glycerin and gelatin, I suppose that he found it sweet and with sound food value.

Last year our neurosurgeon had a surprise. At the end of a craniotomy he asked a nurse to puff his favourite penicillin-sulphanilamide powder into the wound. When she squeezed the bulb, however, a cloud of tiny Egyptian ants emerged. The resulting consternation was mitigated by the bacteriologist, who reported that they were not only sterile but strongly antiseptic. The suggestion that they should in future be sprayed into all wounds has not been followed up.

* * *

My elderly car has just returned to the road after a long illness patiently borne by both of us, and I have been quite touched by people's interest and solicitude.

I used to meet a rubicund man with a large dog every day, and we usually exchanged noncommittal looks, but he waved enthusiastically at my reappearance. A bored-looking woman who is always hanging over her cottage gate, whatever the weather, shouted a greeting. An elderly cyclist, by whose whereabouts on the road I could tell whether I was early or late, made the thumbs-up sign. The butcher in the village grinned and nodded encouragingly as we rattled past his shop. (He once gave me a lift in his van when he saw me panting along towards the hospital at a brisk trot.) And, of course, the porters at the hospital, who had evidently missed my noisy reversings and erratic startings outside their window, came out to admire and congratulate. Even the cows in the fields looked vaguely approving.

The only people who were not sympathetic were the stony-hearted bureaucrats who would not refund the cost of an entirely unused quarterly licence, which ironically enough I had for once renewed in good time.

* * *

She was wearing dark glasses and she said that as she was suffering from nervous debility she thought she would go on the club for a bit. Hoping for a more accurate diagnosis, and to ease my conscience before issuing the inevitable N.I. certificate, I incautiously asked her what she meant by nervous debility. I suppose I deserved her answer: " Well, you're the doctor." I explained that the expression sometimes meant that people were overtired or worried and that it would help me to put things right if she would tell me a little more. " Well, as a matter of fact I've had a blow," she said. " Do you mean the sort of blow you would feel from the loss of a relative, or have you been hit by something? " I inquired. " I've been given a blow by a relative," she replied; and there, as she removed her glasses, was a fine black eye. " You haven't got nervous debility," I said firmly, as I scribbled the Form Med. 1, " you have got a periorbital hæmatoma." I felt better about it that way.

* * *

Thoughts on the N.H.S. while reading to my children:

" Please pass the buck," the Walrus said
And shed a bitter tear.
" You'd think they should have settled this
Instead, they've sent it here.
It's travelled round from him to them
And back again to me
From Records to the Ministry
And to the R.H.B.
Initialled *here* by Tweedledum
And *here* by Tweedledee.

" Please pass the buck," the Walrus said
" A subcommittee call
And make it large and wide enough
To subcommit us all
In case the matter's surgical
The Carpenter shall speak
And every Hatter madly grin
And every Dormouse squeak.
With any luck the meeting will
Go on for half the week."

" Please pass the buck," the Walrus said.
" My conscience must be free.
My pidgin isn't medical,
Admin's my cup of tea.
The Service bids us trim our sails
To all the winds that blow.
Committees are deliberate—
Who dares to call them slow?
For twenty men will say " perhaps "
When any one says " no ".

5. Some were not on any practitioner's list, or were staying only temporarily in the area and thought they could not call on a doctor.

6. A few were dissatisfied with their doctor and wanted a second opinion.

7. A proportion were sent from work or school.

Are these reasons adequate? I doubt if all of them are. In this country everybody is now entitled to a family doctor who should be responsible for his health and welfare. If both the hospital and the family doctor are available for the patient to choose between, the result is duplication of services and weakening of the doctor-patient relationship. Who should decide whether he goes to the casualty department—the patient himself or his doctor? When he is sure that he will be sent on to the casualty department, the patient naturally wants to avoid an unnecessary visit to his doctor first. But, apart from this, some people seem to prefer hospitals to general practitioners.

Use of Casualty by Family Doctor

General practitioners referred cases for various reasons:

1. Trauma, for an X-ray to exclude bony injury, for suture of lacerations, or for treatment of fractures. The X-ray department is not directly accessible to practitioners.

2. Septic cases and a proportion of the surgical cases are referred for minor surgery. Of the septic conditions referred, two-thirds eventually had surgical treatment.

3. Some patients were sent for a second opinion—either directly from the casualty officer or from the outpatient departments to which casualty gives indirect access.

4. Some cases were sent for admission without previous inquiry on whether the hospital had a bed for the patient.

5. In a small but significant number of cases the patient was sent for social reasons. An old lady of 94 arrived with the following note: "Will you please admit this patient. I can find nothing wrong with her except old age". And some acute "psychiatric" conditions were referred to the department, for "social" reasons.

Of these groups the true "casualty" problems were the trauma patients for minor surgery and a small proportion of the cases sent for admission—e.g., overdose of drugs. These amounted to about 60% of the referred cases. The other 40% were a misuse of the casualty department, for they could have been dealt with through other channels.

Future of the Casualty Department

Function.—To have duplication of medical services is both uneconomical and unnecessary. Casualty, like any other service, should have a specific function, and in my view it should deal only with trauma, emergencies (acute medical or surgical cases, 2% in this series), and minor surgery.

Design.—Dependent upon function, the department should be composed of three units—one for trauma, one for minor surgery, and one for emergencies. The trauma unit should have its own beds, and be responsible for inpatient and outpatient care in its specialty.

Staffing.—The casualty department should be under senior hospital medical staff, who would be responsible for supervising and training the junior casualty officer.

Centralisation.—Obviously such a casualty department would not be needed in every hospital. A given area should have its casualty centre at one particular hospital, where it would be maintained and staffed for its special purpose. Centres should be fewer but better: at present many of the casualty departments in this country are staffed by the pre-registration house-physician or house-surgeon on duty—people with no casualty experience.

The future casualty department should not cater for the casual attender. He has his family doctor to consult if he needs medical advice.

Summary

This paper analyses 5000 attendances at a south-east London casualty department. The patients form a consecutuve series seen by one casualty officer.

2935 (60%) were new attendances, and nearly two-thirds of these were casual attenders not referred by a doctor. Only half the new patients were classified as trauma.

In this department the number of new patients has doubled over the past twelve years, though under the National Health Service all patients can go to their family doctor without expense.

The present-day casualty department has no specific function and runs as a "general practice". It is misused to a considerable extent both by the public and by their doctors.

Future casualty departments should have a specific role. Meanwhile more work is necessary both to review existing casualty services and to define their proper function and location.

I should like to thank Mr. L. T. Cotton for permission to conduct this survey, and the casualty reception staff for their valuable cooperation. My thanks are also due to Dr. John Fry for his encouragement and criticism. But the views I express are my own.

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DOCTORS AND NATIONAL SERVICE

THE chairmen of the National Medical Manpower Committee and of the Central Medical Recruitment Committees have issued the following statement:

"The announcement made by the Minister of Labour on Dec. 14, 1959, that certain persons whose deferment for training or study ends on or after June 1, 1960, will not be called up does not apply to doctors or dentists. Doctors liable for National Service have always been dealt with under special and separate arrangements through the three professional committees, which advise on deferments and call-up matters. These special arrangements will continue until the end of 1960, when call-up is planned to end.

"Under these arrangements deferment granted for completion of studies is continued during the pre-registration year, during which all doctors receive a memorandum setting out the arrangements for call-up and for further deferment.

"Doctors who become provisionally registered as medical practitioners on or after Jan. 1, 1960, and doctors granted deferment of call-up to a date beyond the end of 1960 need not, subject to fulfilment of their deferment conditions, expect to be called up except in emergency.

"All other doctors will, if fit, be considered for call-up in the usual way. They will accordingly be nominated for National Service commissions (two years), unless they volunteer to enter the Forces on short service or regular commissions, or unless their call-up is deferred by the Central Medical Recruitment Committees on professional grounds or postponed by the Ministry of Labour on grounds of exceptional hardship.

"In 1960 the Forces will still have substantial requirements for medical officers, which will need to be met largely from doctors liable for National Service. This means that a considerable number of such doctors must expect to be called up during 1960."

In England Now

A Running Commentary by Peripatetic Correspondents

READERS of the best spy stories have long realised that to qualify for the higher echelons of spying a man must be a polished cracksman, a fluent polyglot, and a perfect shot (knife and gun); he must know the odds and modes of cheating at all games of skill and chance; and (if he is a hero) he must also be an appreciative connoisseur of life, for otherwise the Game would hardly be worth the candle—especially as the candle is usually alight at both ends and will be applied to the soles of his feet sooner or later. Of course, if he is a villain, villainy alone is a sufficient motive.

In view of all this literary conditioning, it is doubtful whether there are many people in England who really believe that spies exist. Ours is a land of charming naïveté where evil is concerned—a land of amateurs. We are not accustomed to consider blackmail, perversion, and revenge as common reasons for adopting a profession so inconvenient as intrigue appears to be. We have built up a melodramatic picture of the spy; and, because in our watercolour country we have come to regard as mildly absurd whatever is vivid, we find the idea of the sinister spy either ridiculous or incredible. Probably we shall never be able to assess the evidence on which the accusation was made that a Communist diplomat set afoot the grotesque plan to poison most of the staff of Radio Free Europe by putting atropine in the saltcellars of the canteen. The idea is too fantastic; the English imagination boggles—and then is tempted into a shamefaced chuckle at the notion of several hundred people simultaneously stuffing themselves with deadly nightshade. As like as not, tasteless jokes about the tastelessness of institutional soup will soon become current in student circles, while dons will quote the *Mithridates* passage from Housman or exchange thin-lipped smiles when the cruet passes between the protagonists of some High Table feud.

With our flippant heritage, how can we fail to look on the Bad Man as an object of pity and of decently moderate derision? Anarchists, nihilists, world-dominators, men who hate women, women who hate men, Nazi fascists, inquisitors, Communist fanatics—we are sorry for them. Why do these people make themselves so wretched, we ask first; and then—why must they also try to make *us* wretched? Can it be that for them happiness is harder work than spying, cheating, lying, destroying, torturing? And if this is true for certain individuals, can it also be true for whole nations? And is extremism always destructive; or is there a cause into which it is right to throw all our energies without reservation? Only one suggests itself: the cause of sanity—in other words, of realism, compassion, humour, and truth. These are virtues which never start wars, although, if necessary, they will *wage* war, invincibly.

* * *

Little attention is usually paid to hospital fauna, but ours at least are interesting.

A pet tortoise survived the whole of the war and on its demise was buried outside the operating block. Its tombstone was inscribed with the touching lines:

> " Chloe was a beautiful tortoise,
> Even in rigor mortis "

The other day I went into one of the anæsthetic rooms and found a robin perched on a gallipot pecking away at some K-Y jelly which was used to lubricate airways. As I believe that this substance contains glycerin and gelatin, I suppose that he found it sweet and with sound food value.

Last year our neurosurgeon had a surprise. At the end of a craniotomy he asked a nurse to puff his favourite penicillin-sulphanilamide powder into the wound. When she squeezed the bulb, however, a cloud of tiny Egyptian ants emerged. The resulting consternation was mitigated by the bacteriologist, who reported that they were not only sterile but strongly antiseptic. The suggestion that they should in future be sprayed into all wounds has not been followed up.

* * *

My elderly car has just returned to the road after a long illness patiently borne by both of us, and I have been quite touched by people's interest and solicitude.

I used to meet a rubicund man with a large dog every day, and we usually exchanged noncommittal looks, but he waved enthusiastically at my reappearance. A bored-looking woman who is always hanging over her cottage gate, whatever the weather, shouted a greeting. An elderly cyclist, by whose whereabouts on the road I could tell whether I was early or late, made the thumbs-up sign. The butcher in the village grinned and nodded encouragingly as we rattled past his shop. (He once gave me a lift in his van when he saw me panting along towards the hospital at a brisk trot.) And, of course, the porters at the hospital, who had evidently missed my noisy reversings and erratic startings outside their window, came out to admire and congratulate. Even the cows in the fields looked vaguely approving.

The only people who were not sympathetic were the stony-hearted bureaucrats who would not refund the cost of an entirely unused quarterly licence, which ironically enough I had for once renewed in good time.

* * *

She was wearing dark glasses and she said that as she was suffering from nervous debility she thought she would go on the club for a bit. Hoping for a more accurate diagnosis, and to ease my conscience before issuing the inevitable N.I. certificate, I incautiously asked her what she meant by nervous debility. I suppose I deserved her answer: " Well, you're the doctor." I explained that the expression sometimes meant that people were overtired or worried and that it would help me to put things right if she would tell me a little more. " Well, as a matter of fact I've had a blow," she said. " Do you mean the sort of blow you would feel from the loss of a relative, or have you been hit by something? " I inquired. " I've been given a blow by a relative," she replied; and there, as she removed her glasses, was a fine black eye. " You haven't got nervous debility," I said firmly, as I scribbled the Form Med. 1, " you have got a periorbital hæmatoma." I felt better about it that way.

* * *

Thoughts on the N.H.S. while reading to my children:

> " Please pass the buck," the Walrus said
> And shed a bitter tear.
> " You'd think they should have settled this
> Instead, they've sent it here.
> It's travelled round from him to them
> And back again to me
> From Records to the Ministry
> And to the R.H.B.
> Initialled *here* by Tweedledum
> And *here* by Tweedledee.
>
> " Please pass the buck," the Walrus said
> " A subcommittee call
> And make it large and wide enough
> To subcommit us all
> In case the matter's surgical
> The Carpenter shall speak
> And every Hatter madly grin
> And every Dormouse squeak.
> With any luck the meeting will
> Go on for half the week."
>
> " Please pass the buck," the Walrus said.
> " My conscience must be free.
> My pidgin isn't medical,
> Admin's my cup of tea.
> The Service bids us trim our sails
> To all the winds that blow.
> Committees are deliberate—
> Who dares to call them slow?
> For twenty men will say " perhaps "
> When any one says " no ".

Letters to the Editor

A CENTRAL LABORATORY FOR OCCASIONAL INVESTIGATIONS

SIR,—Dr. Hughes-Davies (Jan. 2) raises the question of how the general physician could gain access to specialised laboratory services, and suggests a national biochemical reference laboratory, on the lines of the bacteriological reference laboratories.

The problem, however, is not quite the same as in bacteriology, either in the pattern of work of such a central laboratory or in the numbers of specimens likely to be submitted, and to establish a worthwhile central laboratory for clinical biochemistry presents formidable problems. Few physicians have any idea of the amount of work which can result from a request which may take only a few seconds to write, and not all physicians would restrict their calls on such a laboratory to the occasions where its help is really necessary. If, for example, the laboratory were to offer to measure urinary catechol-amine excretion, many physicians might come to regard this analysis as part of the routine investigation of hypertension. From the patient's point of view this may be justified, however long the odds may be against finding a significantly increased excretion, but the effect of such requests, on a national scale, would be to make the central laboratory quite unworkable. It is also possible to visualise, in advance, the flood of M.D. theses, both good and bad, which could arise from the work of such a laboratory if it attempted to meet all calls made on it.

A more practicable arrangement might be for each of the larger laboratories in a region to make itself responsible for two or three of the more technically exacting analyses, and for requests to be passed on to these laboratories through local biochemists or clinical pathologists. Unofficial arrangements of this sort already exist in many areas, but to put such arrangements on a more general footing should not be unduly difficult. It is, I think, very desirable that such arrangements should be of a strictly regional character, since otherwise it is hardly practicable for the request to be discussed between the biochemist and the physician concerned, and it is also desirable that physicians should understand the right of the senior laboratory worker to query, and on occasions defer or reject, a request which may take him many hours of work to meet and of whose necessity he is not convinced. Work of this character is not performed by junior technicians, and it is necessary for the man at the bench to be reasonably satisfied that his efforts are not being wasted.

Department of Clinical Chemistry,
Royal Infirmary, Edinburgh. S. C. FRAZER.

SIR,—On the face of it, Dr. Hughes-Davies' suggestion that the National Health Service should establish a central laboratory able to make certain tests on a routine basis appears to be quite good. It does, however, overlook the fact that there are now a large number of group or area laboratories in the National Health Service which are already undertaking most of the tests he has mentioned. There may be some difficulty about hormone investigations requiring maintenance of large stocks of animals, but many biochemical estimations, sometimes regarded as infrequently required, are now routine tests in the larger laboratories. Moreover, many group laboratories have an interchange system whereby a laboratory can supplement its own battery of tests by referring special work not usually done by it to another group laboratory. The suggestion made by Dr. Hughes-Davies also does not take account of the fact that the most important part of a test is interpretation of the result in relation to the patient; expert guidance of this kind is not always easy to obtain from a central laboratory which gives only a postal service.

The Mental Hospitals' Group Laboratory, at West Park Hospital, Epsom, Surrey. W. W. KAY.

CHROMOSOME STUDIES IN LEUKÆMIA

SIR,—In their letter of Oct. 31, Dr. Ford and Dr. Mole make one interesting and justifiable comment on the interpretation of our observations in relation to the occurrence of chromosomal abnormalities in human leukæmia. We would agree that it is possible that the absence of chromosome abnormalities in our cultures of marrow from patients with one or other type of chronic leukæmia is due to the leukæmic cells not having divided in culture. This being so, the cells of an apparently normal chromosome constitution which we observed would be derived from normal marrow elements. It is now possible, however, to test if any unusual numbers of cells were present in these cultures with chromosome counts differing from the modal number by calculating the expected numbers of cells with typical and atypical (non-modal) counts and comparing these numbers with the observed numbers.[1] If a small but significant excess of atypical cells were present there would be some justification for believing that we were observing some abnormal leukæmic cells but, because of their small number, classifying them as artefacts. We have now made such calculations for 8 cases of chronic leukæmia (5 of chronic myeloid and 3 of chronic lymphatic) inclusive of the cases reported in our paper (table I). From these calculations it can be seen that there is no difference between the expected and observed numbers of non-modal cells in the marrows from patients with chronic lymphatic leukæmia. In those from patients with chronic myeloid leukæmia there is a small excess of atypical cells but this may well be due to the play of chance ($\chi^2 = 2{\cdot}40$, $P > 0{\cdot}1$).

We feel, therefore, that, if the cells of chronic leukæmia carry a chromosomal abnormality, the abnormality may be of such fineness as to be below the visual threshold of our technique. We cannot exclude, however, the possibility that visible abnormalities may occur but remain hidden from us because either the culture times are too short or the conditions of culture are harmful to these types of cell.

Medical Research Council Group for Research on the General Effects of Radiation, Western General Hospital, Edinburgh. A. G. BAIKIE
W. M. COURT BROWN
PATRICIA A. JACOBS.

WHAT TO EXPECT FROM OUR BABIES

SIR,—The reader of your annotation of Jan. 2, dealing with a recent special report of the Medical Research Council, might legitimately conclude, if he had not had the opportunity of studying this interesting report, that the author's claim to have established weight standards for the first year of life, according to birthweight, based on examinations of over 700 infants.

Although reasons are given in the report for assuming that the 15% of cases remaining in the sample at the age of 8–12 months is representative of the sample as a whole, it would not seem reasonable to accept as standards mean weights based, for example, at 5–6 months on 5 cases in the 2–3 lb. birthweight group, 8 in the 3–4 lb., and 23 in the 4–5 lb. groups. Nor can it be said that the findings in this report

1. Court Brown, W. M., Jacobs, P. A., Doll, R. *Lancet*, Jan. 16, 1960, p. 160.

disprove the supposition that many infants smaller at birth remain at the lower end of the normal weight scale.

Current studies in Edinburgh indicate that the prematurely born tend to remain smaller than average in the preschool period, and though this can be attributed in part to less favourable environment and small parental stature, many of those in the 2–3 lb. birthweight group remain markedly undersized well into the school-age period, even when there is no obvious effect of environmental or genetic factors. In these cases at least " the accident of gestational age " appears to have a marked effect on the " inborn pattern of body size."

Department of Child Life and Health, University of Edinburgh. C. M. DRILLIEN.

MEDICAL JOURNALS FOR DOCTORS IN DEVELOPING COUNTRIES

SIR,—Your account (Jan. 2) of the scheme which is being started to enable British doctors to send their medical journals on to colleagues oversea is doubly gratifying; first, because of the excellent project that you describe; secondly, because you refer to *developing* countries and only permit " underdeveloped " to appear between quotation marks. It has become customary to refer to " underdeveloped countries ", but this is scarcely a satisfactory designation. There are many underdeveloped countries, such as Australia, which are not being referred to, and the phrase has a rather unpleasantly patronising flavour. I therefore hope that others will follow your example, and that " underdeveloped " will no longer be used to designate newly developing countries.

St. Paul's Cray, Orpington, Kent. L. M. FRANKLIN.

THE COST OF DRUG TREATMENT

SIR,—The article in your issue of Jan. 2 by Dr. Miller and Dr. Smith is full of most useful information and, in general, appears to be an objective report on a problem which has, in many other quarters and on many occasions, been treated in anything but an objective manner. There are, however, features of the article to which I feel that further attention should be drawn, particularly as those features have led to quotation (or misquotation) in the *Daily Express*.

The feature to which, from the pharmaceutical standpoint, the greatest exception is taken is the quoting of the " basic cost " per week of phenobarbitone therapy and the development from it of the contention that the chemist-contractors' remuneration increases the cost by more than 1600%. If I were to contend that on each patient whom a medical practitioner has on his list and who requires no attendance or other service during the year, the medical practitioner makes an astronomical *percentage* profit I would be just as accurate but just as unfair as Dr. Miller and Dr. Smith.

They also draw attention to the fact that in their calculations a flat-rate dispensing fee of 1*s.* 2*d.* has been added to the basic cost " but that in fact this is the minimum ". By quoting one higher fee of 4*s.* 0*d.* they imply that the minimum fee is not the fee usually met with. In fact, the national average dispensing fee, assessed over 200,000,000 prescriptions, is 1*s.* 2·8*d.*; and it should be noted that that level of remuneration was only conceded by the Ministry of Health after the most exhaustive costing investigations and subsequent " negotiations " in which figures to the fourth place of decimals featured prominently and in which all increases in salaries and overhead costs which have occurred since 1956 were completely disregarded.

As to the contention of Dr. Miller and Dr. Smith that because " rather more than three-quarters of all National Health Service prescriptions are for tablets " their " dispensing does not call for any high degree of professional skill ", they are, in my view, adequately and best answered by the fact that (as the Minister of Health has, himself, said) " the role of the pharmacist is vital in the handling of these products " and has led to an increase in the severity of the educational standards required for entry into and subsequent qualification in the pharmaceutical profession.

H. NOBLE
Secretary, Central N.H.S. (Chemist-Contractors) Committee.
London, W.C.1.

THROMBOTIC THROMBOCYTOPENIC PURPURA

SIR,—Dr. Bernstock and Dr. Hirson's paper of Jan. 2 quotes several examples from the literature. Presumably because the paper was written before our case was published [1] they have not had an opportunity to comment on that. This might be an opportunity to point out that our child, who was $2^1/_2$ years of age at the onset of the disease, completely recovered, following a five-week course of cortisone. There was no clinical or hæmatological relapse subsequently, and to date, two years after his admission, he is a perfectly normal little boy.

The University of Sheffield Department of Child Health, The Children's Hospital, Sheffield. J. LORBER.

PROPHYLAXIS IN THROMBOEMBOLISM

SIR,—In a leading article on Dec. 5 you stated: " What little theoretical understanding we do have is still based on the triad of causes enunciated with extraordinary vigour and lucidity by Virchow . . ." It is probably that because it was said with vigour by a master we cling to this concept and give little attention to other probable explanations.

It can be stated with considerable assurance that two of the factors of the triad—namely, altered coagulability of the blood and impaired circulation—are rarely, if ever, primary in the causation of intravascular clotting. In fact, it is still a moot question whether hypercoagulability has ever been unequivocally demonstrated. Progress in understanding thrombosis and abnormal bleeding has been hampered perhaps more by the myth that the clotting-time is a measure of physiological coagulability than by any other theory of coagulation.

Coagulability implies formation of thrombin, and the defence against massive intravascular clotting is the prompt removal of this clotting factor from the circulating blood. In a recent study, my associates and I [2] have reconfirmed the observation that when thrombin is injected intravenously at a slow steady rate, it does not cause thrombosis. We offer the explanation that thrombin is promptly removed by adsorption to the surface of fibrin fibrils which are rapidly removed from the circulating blood.

The thrombin that gives rise to a pulmonary embolus is generally regarded as having its origin in the peripheral venous system. It has been postulated [3] that it may be initiated by a localised injury of a vessel wall. Such an injury liberates enough tissue thromboplastin to cause the formation of the primary clot attached to a vessel wall. When this clot retracts, it expresses a serum rich in nascent thrombin. If this serum is not promptly swept into the circulation, a secondary clot attached to the primary thrombus is produced. By a multiple repetition of this process, the thrombus grows in the direction of the blood-stream and when dislodged from its mooring becomes a pulmonary embolus.

The success of anticoagulant therapy, as again convincingly demonstrated by the excellent paper of Sevitt and Gallagher,[4]

1. Lorber, J., Emery, J. L. *Proc. roy. Soc. Med.* 1959, **52**, 301.
2. Quick, A. J., Hussey, C. V., Harris, J., Peters, K. *Amer. J. Physiol.* 1959, **197**, 791.
3. Quick, A. J. *Practitioner*, 1951, **166**, 213.
4. Sevitt, S., Gallagher, N. G. *Lancet*, 1959, ii, 981.

can be explained satisfactorily by the above theory. The prompt neutralisation of thrombin by heparin or the depression of the thrombinogenic activity of the blood by a drug decreasing prothrombin activity effectively prevents the growth of the thrombus because the clotting activity of the expressed serum is greatly reduced by either agent.

Marquette University, Milwaukee, Wisconsin. ARMAND J. QUICK.

THE NATURE OF ESSENTIAL HYPERTENSION

SIR,—In your review (Jan. 2) of *Medical Surveys and Clinical Trials*, edited by L. J. Witts, you say: "Once again the professional habit of dividing normal from abnormal systolic blood-pressure at about 160 mm. Hg appears to be reasonable." I would be greatly obliged if you or any of your readers would furnish me with the evidence on which this statement is based.

Oxford. G. W. PICKERING.

*** The evidence was discussed in our leading article of Nov. 21 and the letters we have since printed. Sir George interprets our review as suggesting that the issue is settled—which would certainly be going too far. The customary division between normal and abnormal pressures was described only as "reasonable".—ED. L.

CASE-FATALITY IN TEACHING AND NON-TEACHING HOSPITALS

SIR,—In 1957 we showed [1] that there was a higher case-fatality for certain conditions in non-teaching hospitals than in teaching hospitals. This study was based on the data collected by the General Register Office in the national Hospital Inpatient Morbidity Enquiry for England and Wales in 1951 and in 1953–54. The collection of data has continued, and that for 1955 has recently been published.[2 3] We have tried to analyse this new material, together with some additional unpublished data supplied by the General Register Office and the Ministry of Health, in the same way as the earlier.

TABLE I—NUMBER OF CASES OF HYPERPLASIA OF PROSTATE, NUMBER OF DEATHS AND CASE-FATALITIES IN TEACHING AND NON-TEACHING HOSPITALS, 1953–54 AND 1955 (MEN AGED 45 YEARS AND OVER)

—	1953–4		1955	
	Teaching hospitals	Non-teaching hospitals	Teaching hospitals	Non-teaching hospitals
Cases	290	729	112	671
Deaths	12	70	4	101
Case-fatality	4·1%	9·6%	3·6%	15·1%
Case-fatality standardised for age and mode of admission*	4·1%	7·8%	3·6%	11·3%
	(P<0·05)		(P<0·05)	

* Using the age structure, and the proportion of "immediate" admissions, of the teaching hospital cases in each period as the "standard" population.

As time passes, the General Register Office and the Ministry of Health are able to make the Hospital Inpatient Morbidity Enquiry more representative. The 1955 material includes effectively random samples of the patients discharged from very large numbers of non-teaching hospitals, including those of two complete regions, and from nearly half the teaching hospitals in England and Wales. However, the use of the same sampling fraction (10%) for both teaching and non-teaching hospitals means that in many conditions the number of cases and deaths reported by the teaching hospitals is very small. Because of this the data for appendicitis and for diabetic coma, for both of which there was a marked difference in the experience of teaching and non-teaching hospitals in the earlier study, cannot usefully be analysed for 1955. But there were enough cases and deaths from hyperplasia of the prostate and from perforated peptic ulcer in the 1955 material for analysis in some detail.

TABLE II—NUMBER OF CASES OF PERFORATED PEPTIC ULCER, NUMBER OF DEATHS AND CASE-FATALITIES IN TEACHING AND NON-TEACHING HOSPITALS, 1953–54 AND 1955 (MEN OF ALL AGES)

—	1953–4		1955	
	Teaching hospitals	Non-teaching hospitals	Teaching hospitals	Non-teaching hospitals
Cases	144	280	52	240
Deaths	12	33	9	31
Case-fatality	8·3%	11·8%	17·3%	12·9%
Case-fatality standardised for age*	8·3%	9·8%	17·3%	10·6%
	(P>0·05)		(P>0·05)	

* Using the age structure of the teaching hospital cases in each period as the "standard" population.

Hyperplasia of the Prostate

Case-fatalities in the two types of hospital in 1955 are shown with those of 1953–54 for comparison, in table I. There is a significantly lower case-fatality among the teaching-hospital patients (3·6% compared to 15·1%). The different age-distribution of patients in the two types of hospital, and the different proportions of "immediate" or emergency admissions to them have made little contribution to this difference in case-fatality as is shown by its persistence (3·6% and 11·3%) when these factors are allowed for by simple standardisation.

Some cases admitted to hospital with *retention of urine* were given no more specific diagnosis; they will certainly have included men with hyperplasia of the prostate. For the period 1953–55, there were 49 such male cases aged over 45 reported by teaching hospitals, and 304 by non-teaching hospitals. The case-fatality among these patients, when standardised for age and mode of admission in the same way as the cases definitely described as suffering from hyperplasia of the prostate, was 4·1% in the teaching hospitals and 15·0% in the non-teaching hospitals. The relatively greater use of this less precise diagnosis by non-teaching hospitals cannot therefore have produced the observed difference in case-fatality in hyperplasia of the prostate.

The death rate from hyperplasia of the prostate in England and Wales as a whole fell by 27% between 1951 and 1957.[4] There are no data on case-fatality later than 1955, but clearly the analysis of the 1956 and 1957 results of the Inpatient Morbidity Enquiry will be very interesting.

Perforated Peptic Ulcer

In 1951–54 case-fatality from perforated peptic ulcer was somewhat higher in the non-teaching hospitals. This difference was small and it was less regular than for hyerplasia of the prostate.

There were just sufficient numbers of cases and deaths from this condition reported in 1955 for separate analysis. The

TABLE III—NUMBER OF SURGEONS PER 1000 SURGICAL BEDS, IN TEACHING AND NON-TEACHING HOSPITALS, NATIONAL HEALTH SERVICE, ENGLAND AND WALES, 1958

Staff	Teaching hospitals	Non-teaching hospitals
Consultants	26	17
Senior hospital medical officers	0·3	1·8
Senior registrars	18	2·2
Registrars, junior hospital medical officers	29	22

This table includes all surgeons appointed in general surgery, traumatic and orthopædic surgery, urology, plastic surgery, thoracic surgery, and neurosurgery; and all staffed beds in these specialities.

1. Lee, J. A. H., Morrison, S. L., Morris, J. N. *Lancet*, 1957, ii, 785.
2. General Register Office (1959) Statistical Review of England and Wales, 1955; Supplement on Hospital Inpatient Statistics. H.M. Stationery Office.
3. *Lancet*, 1959, ii, 416.
4. General Register Office. Unpublished.

TABLE IV—NUMBER OF ANÆSTHETISTS PER 1000 SURGICAL BEDS IN TEACHING AND NON-TEACHING HOSPITALS, NATIONAL HEALTH SERVICE, ENGLAND AND WALES, 1958

Staff	Teaching hospitals	Non-teaching hospitals
Consultants	18	10
Senior hospital medical officers	0·7	2·7
Senior registrars	5·8	0·6
Registrars, junior hospital medical officers	20	8·9

Surgeons and anæsthetists employed part-time in any of the above grades have been converted to a whole-time equivalent on the basis of 38½ hours per week.

result of this is given in table II. The advantage in 1955 lay with the *non-teaching* hospitals. Such a reversal suggests that there is no real difference between the case-fatalities from perforated peptic ulcer in the two types of hospital.

Staffs of the Two Types of Hospital

In our earlier paper we commented on the substantial differences in the staffing ratios of teaching and non-teaching hospitals. Figures for 1958–59 have kindly been made available to us by the Statistical Division of the Ministry of Health (tables III, IV, and V). There has been little change since 1953. Data on numbers of house-officers in the two kinds of hospital are not available for 1958. No regional analysis has yet been attempted.

Characteristics of Patients

The point was made in correspondence [5] on our original paper that the social class of patients may affect their prognosis to an important extent, and that the distribution of patients by social class was likely to be different in the two types of hospital. Unfortunately, the General Register Office were unable to obtain the current, or most recent, occupation (whence "social class" is derived) from hospitals in 1951–55 for more than a

TABLE V—NUMBER OF NURSES PER 100 BEDS IN TEACHING AND NON-TEACHING "ACUTE" AND "MAINLY ACUTE" GENERAL HOSPITALS, NATIONAL HEALTH SERVICE, ENGLAND AND WALES, 1959

Full-time		Part-time	
Teaching hospitals	Non-teaching hospitals	Teaching hospitals	Non-teaching hospitals
84	49	3	12

No data are available on the distribution by surgical or medical beds, or on the whole-time equivalent of part-time nursing staff.

small proportion of the patients. We hope to be able to study this question later as a renewed attempt is being made to collect data on occupations.

We are also making a more detailed study, in collaboration with one regional hospital board and board of governors, of their patients with hyperplasia of the prostate. Information about the occupations will be available. An attempt is also being made to classify patients by their clinical condition before operation, and to analyse postoperative morbidity as well as mortality in the two types of hospital.

Beds for the Chronically Ill

The possibility is sometimes raised that the presence of beds for the chronically ill in the non-teaching hospitals may increase their case-fatalities for such conditions as hyperplasia of the prostate,[6] and that these may also influence the staffing ratios and make their interpretation difficult. The data in the Hospital Inpatient Enquiry are based on the patient's total duration of stay, without regard to transfers *within* the hospital. The number of long-stay patients in the non-teaching hospitals discharged or dying with a diagnosis of hyperplasia of the prostate cannot be large, for the durations of stay with this diagnosis are similar in the two types of hospital. Moreover, it has already been shown that the extra mortality in the non-teaching hospitals could not be accounted for by such long-stay patients as they did have.[1] The ratios of surgeons and anæsthetists are of course calculated per 1000 *surgical* beds, and are unaffected by the presence or absence of other types of accommodation, such as beds for the chronically ill, in the hospital. The ratio of nurses to beds (table v) is in fact closely similar in non-teaching hospitals whether they are altogether "acute" or "mainly acute".

We are grateful to the General Register Office and the Statistical Division of the Ministry of Health for their help.

J. A. H. LEE
S. L. MORRISON
J. N. MORRIS.

Social Medicine Research Unit of the Medical Research Council, London Hospital, E.1.

5. Platt, R. *Lancet*, 1957, ii, 893.
6. General Register Office Statistical Review of England and Wales, 1955; Supplement on Hospital Inpatient Statistics; p. 21. H.M. Stationery Office, 1959.

THE CONVALESCENT EXCRETER OF SALMONELLÆ

SIR,—Dr. Schrire (Jan. 2) is unduly optimistic when he reports that few patients continue to carry *Salmonella typhimurium* or other intestinal pathogens after treatment. In my experience the antibiotics so far available seem to have little effect on the salmonella carrier, nor does furazolidone fare better. At Coppetts Wood Hospital 11 patients suffering from salmonella food-poisoning were treated with antibiotics (tetracycline, chloramphenicol, or streptomycin) and at the end of the course 9 continued to excrete the organism. A further 7 patients were treated with furazolidone but with no greater success, for all became convalescent carriers. The results of treating 8 cases of Sonne dysentery with furazolidone were equally disappointing, for in each case we obtained positive stool-cultures on completing treatment. With such uniformly poor results furazolidone would appear to be of little value in treating the human salmonella carrier or the carrier of *Shigella sonnei*.

Coppetts Wood Hospital, Muswell Hill, London, N.10. RONALD T. D. EMOND.

THE ABNORMAL APPENDIX

SIR,—In his helpful and readable article of Dec. 26, Mr. Jewers reiterates the feasibility and importance of early diagnosis and removal of the acutely inflamed appendix. This general diagnosis covers a variety of clinical pictures, each dependent on the position of the inflamed organ and with its own particular differential diagnosis.

While one cannot quarrel with Mr. Jewers' paramedian incision, I suggest that easy and adequate approach can equally be by appropriate incision over the inflamed organ: high muscle split in the flank for retro- or para-cæcal, transverse pararectal with lateral muscle-split extension and preservation of intercostal nerve and inferior epigastric blood-vessels for tethered retromesenteric and iliac, and lower midline for pelvic, or where peritonitis has developed. Diffuse peritonitis is treated by early placement of damp mops, changed at intervals during the operation until they come out apparently clean, and the abdomen is closed without drainage.

Transperitoneal drainage with a red-rubber tube of a localised inflammatory mass may be likened to the gastroscopic investigation of a wasps' nest on a drowsy summer afternoon, and may be the cause of fæcal fistula and adhesions.

Acute intestinal obstruction, either of the small gut or of the appendix by a stercolith, is not amenable to conservative treatment. The tethered retromesenteric inflamed appendix in particular must be removed early in order to forestall retromesenteric peritonitis, lower small-gut obstruction, and portal pyæmia.

Mr. Jewers' paper and his references are worthy of study.

Royal East Sussex Hospital, Hastings, Sussex. J. A. KERR.

EARLY DIAGNOSIS OF PREGNANCY

SIR,—I was very interested to read Dr. Foster's letter [1] on the early diagnosis of pregnancy using 'Disecron' and in Dr. Hobson's doubts.[2]

I should like to mention a test for the early diagnosis of pregnancy which I described in 1954. At that time, we first examined the cervical mucus to find out whether crystallisation "like fern leaves" took place, but we have now modified the method and give straight away 2 mg. of œstradiol benzoate and 50 mg. of progesterone together intramuscularly.

We have used the method in more than 350 cases of delayed menstruation, and results have been excellent. Two to eight days after the injection in all cases of non-pregnancy menstruation appears, and in all pregnancies no menstruation follows.

Dr. Hobson objects to the injection of steroid material because "we cannot be certain that the resulting hormonal imbalance, however small, may not itself cause an abortion in susceptible women". But, in my experience, exactly the opposite happens. The steroids seem to have a beneficial effect on the fertilised ovum in women of low fertility by modifying the endometrium favourably.

After more than 350 tests, the accuracy of the method using 2 mg. of œstradiol benzoate and 50 mg. of progesterone is better than the Aschheim-Zondek test (especially when frogs are used). The test is reliable, economical, and practical.

Toronto. L. G. POLYMENAKOS.

AN ILLNESS OF INFECTION IN CHICKENPOX

SIR,—An "illness of infection" was first recognised in measles by Goodall [3] in 1925. He described 4 patients who had a transient febrile illness within a day or two of exposure to measles. This was followed by a period of apparently normal health before the usual prodromal symptoms and measles rash appeared. Since that time over 30 cases have been reported in the literature. It is estimated that about 10% of patients with measles have an illness of infection. It has also been recognised that a small proportion of patients have symptoms throughout the incubation period.[4]

It is quite possible that similar phenomena occur in other infectious diseases but the symptoms or clinical features are so mild that they escape notice. Recently an opportunity arose to test this in chickenpox.

One day the eldest boy (aged 11) of a family developed malaise, generalised aches and pains, and fever. Next day he had a characteristic chickenpox rash. Twice-daily oral temperatures were taken from all members of the family for the next 15 days. No attempt was made to isolate the child.

The temperature records are shown in the accompanying figure. The first record is that of case 1, the boy already described. Case 6, the father, had previously had chickenpox, and his temperature stayed below 98·6°F for the whole of the observation period. All the rest of the family had typical chickenpox in due course. Case 5, the mother, had a temperature of 99·6°F in the evenings of the third and fourth days of case 1's illness. During the same period the other children had at least one temperature recording of 99°F, and case 4 had a reading of 99·6°F. None of them complained of symptoms. Thereafter the temperatures of cases 3, 4, and 5 remained below 99°F until the fever began before the rash appeared.

Case 2, a girl of 7 years, showed a slightly different pattern. She had a temperature of 99°F or over on the third, fourth, seventh, and tenth days of the incubation period before prodromal fever developed.

These observations are clearly no more than preliminary and suggestive. Their interest, if confirmed, is at least threefold. First, it may be possible to identify a few more of the many unexplained fevers. Second, when known exposure has occurred, it may be possible to predict that a particular person will develop the disease (the converse is not true). Lastly, these small rises of temperature provide some clinical support for the pathogenesis of the acute specific fevers outlined by Fenner.[5]

Fenner suggested that first there is a local invasion of the body by the virus. This is followed by a viræmia. The virus then settles in the viscera, probably in the reticuloendothelial system. It multiplies here during the incubation period and then issues forth in a further viræmia or series of viræmias. These, together with peripheral invasion of the skin, respiratory tract, &c. are responsible for the customary clinical features of the disease. In this view the illness of infection represents the first viræmia or systemic spread of the organism.

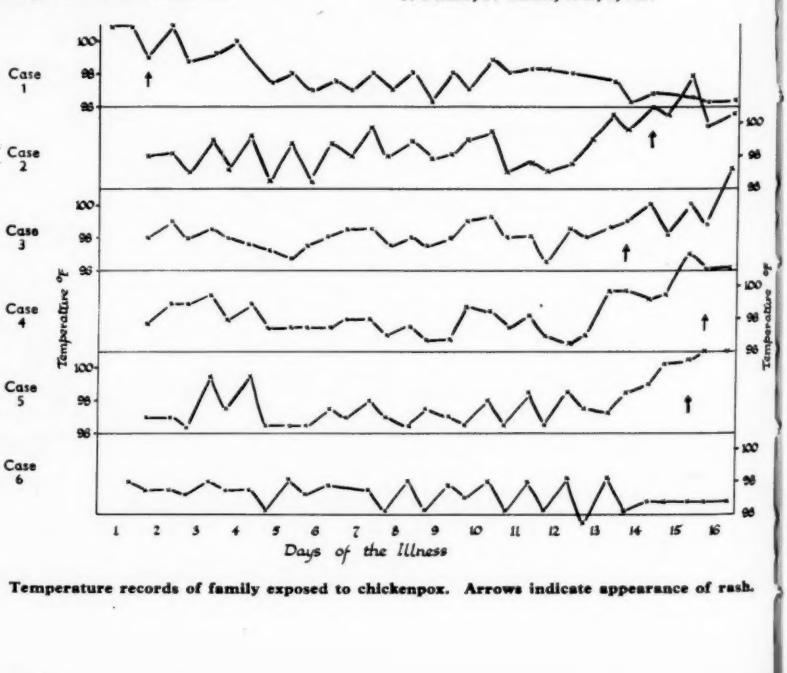
Fenner's theory was based on laboratory work with mousepox. Clinically, the onset of measles is consistent with his hypothesis. The present findings suggest that a similar train of events could well occur in chickenpox.

It should be possible to confirm or refute these observations by taking the temperatures of all exposed persons during an outbreak of chickenpox in other families, hospitals, nurseries, or schools.

I wish to thank Mr. T. Foster of the Royal Infirmary, Sheffield, for the figure, and my family for being such patient guineapigs.

Toronto. M. W. PARTINGTON.

5. Fenner, F. *Lancet*, 1948, ii, 915.



Temperature records of family exposed to chickenpox. Arrows indicate appearance of rash.

1. *Lancet*, 1959, ii, 242.
2. *ibid.* p. 409.
3. Goodall, E. W. *Clin. J.* 1925, **54**, 69.
4. Partington, M. W., Quinton, J. F. P. *Arch. Dis. Childh.* 1959, **34**, 149.

EMERGENCY RESUSCITATION IN RUPTURED ECTOPIC GESTATION

SIR,—Mr. Azie (Dec. 12) is to be congratulated on his successful treatment of a formidable case of ruptured ectopic pregnancy in difficult circumstances, and for advocating the method of autotransfusion which is so much neglected in this country nowadays.

It is surely the ideal method of transfusion—the blood is perfectly compatible, it has been kept at body-temperature, it is to some extent defibrinated, it needs little or no anti-coagulant, and, as Dr. Burrowes (Dec. 26) has told us, it is acceptable to a Jehovah Witness. The modern generation in this country has lost sight of the method, or more probably has never known it: one recalls the story of the evacuee child at the beginning of the late war who said after seeing a cow milked that at home they didn't get milk like that but out of a nice clean bottle. The increasing use of suction in theatres also perhaps tends to discourage it.

I have found that the easiest way to collect the blood is to have a borrowed soup ladle sterilised with the instruments, but the main difficulty nowadays is to find a suitable container to put the blood in. While perhaps the method is indicated only in the fulminating sort of case described by Mr. Azie and Professor Chassar Moir (Jan. 2) with a massive hæmorrhage, it would be unfortunate if the method were to fall into disuse in this country, and it is time we realised that we cannot always expect to live in a perpetual lotus-land, with, among other things, endless supplies of preserved blood easily available.

Middlesbrough. BRYAN WILLIAMS.

SIR,—Mr. Azie's letter reminded me of the early post-war years when blood-transfusion facilities were very poor even in large surgical centres in Greece. At that time it was the rule to try to retransfuse as much of the intra-abdominal blood as possible, and this procedure has been used at the Athens State General Hospital not only in cases of ruptured ectopic gestation but in every case of intraperitoneal hæmorrhage.

I remember a patient with a stab wound who immediately after the opening of his abdomen under local anæsthesia received more than 200 ml. of his own blood before it became evident that his stomach had a perforating wound from which gastric juice was leaking out. The patient developed no reaction whatsoever after this erroneous autotransfusion, and under penicillin cover only he made the smoothest post-operative recovery.

During the same period we also used autotransfusion successfully during aseptic major operations involving accidental or inevitable profuse intraperitoneal bleeding.

As Mr. Azie states, "this simple method could be applied by any doctor with little or no assistance in a remote hospital". I would add that although this method should be in the mind of every surgeon it should not be used when blood-transfusion facilities are available or when the aseptic condition of the intraperitoneal blood is suspect because of an intestinal injury or otherwise.

Laikon Hospital, Athens. N. J. GEORGIADIS.

SIR,—It was very pleasing to read the letter from Sir Claude Frankau in your last issue, for at that time I was in Bethune and was shifted as surgical specialist to the 7th Div. clearing station at Aire close by.

At the battle of Neuve Chapelle in March, 1915, and later in that of September 25, we who drained the front line opposite us, regularly used peritoneal blood for resuscitation and thought little of it, for the simple reason that for long prior to the war in my own hospital, the Eden, Calcutta, it was a hospital standing order that in every case where blood from whatever cause was extravastated into the abdomen, it should, after filtering, be reintroduced into the blood-stream. The only obligation being in those days that the vessel to contain the blood should contain not less than 1 oz. of 1% sodium citrate solution, and that the actual blood that was "cupped" from the belly should be filtered through not less than 12 layers of plain white gauze.

I can recall hearing of Captain Fraser's success at Bethune but in the flurry of war it raised no eyebrows in the Meerut C.C.S. of Major Goodwin, for very shortly after, we were all waiting on the very original work of Kenneth Walker who had initiated direct blood-transfusion.

Looking back over the years and recalling the tragedy of the Battle of Loos, I have no doubt whatever that we saved many lives by what in those days were dubbed by Lilliputians, "Oriental ways".

London, W.1. V. B. GREEN-ARMYTAGE.

EVENING COLIC IN INFANTS

SIR,—Dr. Tuckman's criticism (Jan. 2) of the figures for the dicyclomine study are legitimate, but they omit certain other relevant data.

To reiterate, of 16 babies receiving the inert substance, 8 were unaffected, and the remaining 8 were given a total score of 19, the mean score being +1·18. Of 20 receiving the active drug, only 1 was unaffected, the remaining 19 being given a total of +47, the mean score being +2·35.

Three mothers found the inert substance more effective than the active drug, the total difference being +5. Nine mothers found the active substance better than the inert one, the total difference being +20.

Five mothers stated that one bottle was useless, and the other very effective, and in each case the one considered useless contained the inert substance.

I think that my conclusion that the drug is of value is justified.

The University of Sheffield
Department of Child Health,
The Children's Hospital,
Sheffield. R. S. ILLINGWORTH.

INTESTINAL ABSORPTION OF VITAMIN B_{12}

SIR,—The paper [1] by Reizenstein and Nyberg on the intestinal absorption of liver-bound radiovitamin B_{12} was of especial interest to us in relation to current studies in our laboratory with 5, 6-dimethylbenzimidazolyl cobamide coenzyme ("coenzyme B_{12}").*

Barker's group, which isolated this material from liver, presented evidence suggesting that this coenzyme B_{12} may be the metabolically active form of vitamin B_{12} as well as the main storage form in the liver.[2] The possibility was raised that this material might be absorbed from the intestine more readily than vitamin B_{12} in the absence of intrinsic factor.

Our preliminary studies with "coenzyme B_{12}" suggest that:

(1) In vitro, coenzyme B_{12} appears to compete with vitamin B_{12} in a 1:1 ratio for attachment to intrinsic factor on liver homogenate receptors.

(2) Patients with pernicious anæmia in relapse show optimum hæmatological and clinical responses to the daily intramuscular injection of 1 μg. of either coenzyme B_{12} or vitamin B_{12}. At this intramuscular dosage level, coenzyme B_{12} and vitamin B_{12} appear equal in their effects.

(3) The absorption of small (2 μg.) oral doses of radioactive coenzyme B_{12}† appears to be less dependent on intrinsic factor than the absorption of similar doses of vitamin B_{12} itself as suggested by our preliminary studies with Schilling-type testing [3] using ^{58}Co coenzyme B_{12}.

* Supplied to us by Dr. H. A. Barker, Department of Biochemistry, University of California, Berkeley 4, California, and Dr. David Perlman, Squibb Institute for Medical Research, New Brunswick, N.J.

† The radioactive ^{58}Co coenzyme B_{12} was obtained through the courtesy of Dr. David Perlman, Squibb Institute for Medical Research, New Brunswick, N.J.

1. Reizenstein, P.G., Nyberg, W. *Lancet*, 1959, ii, 248.
2. Weissbach, H., Toohey, L., Barker, H. A. *Proc. Nat. Acad. Sci.* 1959, **45**, 521.
3. Ellenbogen, L., Williams, W. L. *Blood*, 1958, **13**, 582.

We would speculate that the liver-bound B_{12} of Reizenstein and Nyberg and coenzyme B_{12} of Barker may be the same substance. Further studies are indicated to test both this possibility and the possibility that coenzyme B_{12} may be less intrinsic-factor-dependent for intestinal absorption than vitamin B_{12} itself.

LOUIS R. WASSERMAN
SOLOMON ESTREN
EUGENE BRODY
VICTOR HERBERT.

New York City.

RADIOLOGY IN PERNICIOUS ANÆMIA

SIR,—We should like to correct two points in your annotation " Gastric Outline and Motility " (Jan. 2) concerning our radiological findings in the stomach in pernicious anæmia. On examining 69 patients with pernicious anæmia in remission we found, in 53, a combination of features which we believed indicated gastric atrophy (not gastritis). These were, as stated, a smooth tubular longitudinal gastric segment, a smooth fundus devoid of normal folding, fine " crushed tissue-paper " rugæ in the empty longitudinal part of the stomach with normal rugal pattern in the transverse part. The stomachs were of small volume and emptied rapidly so that they could not be distended. This was partly due to the peristalsis which was quite active and not poor, as stated in your annotation. We think this point is important because in the only case in the series where peristalsis was absent in the body of the stomach a " leather bottle " type of carcinoma of the stomach was present. Details of the findings in these patients with pernicious anæmia and in the control group are awaiting publication.[1]

Radiodiagnostic Department,
Hammersmith Hospital,
London, W.12.

J. W. LAWS
R. G. PITMAN.

OBESITY

SIR,—Dr. McMullan in his letter of Jan. 2 writes: " There is nothing inherently improbable in the idea that certain people—even most people—are able to respond to excessive food intake by increased metabolism." This thesis was set out nearly 50 years ago by Grafe,[2] who postulated such a *luxus Konsumption* mechanism: since then, it has been widely discussed but has received no satisfactory experimental support. I used to think that it was probably correct and five years ago with some colleagues tried to get good evidence to confirm the thesis.

We[3] gave three constitutionally thin young men diets containing 1300–1600 calories in excess of their requirements for periods of 10–14 days. During this time they followed a standard regime in a metabolic ward. Metabolic-rates were determined by indirect calorimetry at 4-hourly intervals throughout 24-hour periods. There was no evidence that any of the excess food was oxidised, apart from a small amount due to the rise in metabolism attributable to the specific dynamic action of the extra protein eaten. There can be no doubt that these three young men possessed no *luxus Konsumption* mechanism.

In the continued absence of any positive experimental support for this thesis, it seems unlikely that normal people possess an ability to metabolise directly any dietary excess.

Department of Physiology,
University of Edinburgh.

R. PASSMORE.

1. Laws, J. W., Pitman, R. G. *Brit. J. Radiol.* 1960 (in the press).
2. Grafe, E., Graham, D. *Hoppe-Seyl. Z.* 1911, **73**, 1.
3. Passmore, R., Meiklejohn, A. P., Dewar, A. D., Thow, R. K. *Brit. J. Nutr.* 1955, **9**, 20.

POSTOPERATIVE DIARRHŒA

SIR,—Mr. Shipman (Dec. 12) points out that, once diarrhœa has commenced, the transit time of methylene-blue through the bowel is shortened.

The transit time should be accepted with caution, owing to the rapidity with which methylene-blue diffuses through a liquid medium. The only explanation of the continuing dilatation of the bowel in these patients is the presence of some degree of " hold-up " or stasis of the intestinal contents.

But it is the state of the bowel before the onset of the diarrhœa which is important from the ætiological point of view. In my cases, there was a highly significant association between intestinal stasis and the subsequent development of diarrhœa. During the period of stasis, constipation was almost invariable, so it was not possible to estimate the transit time through the bowel.

Victoria Infirmary,
Glasgow.

GRAHAM SCHOFIELD.

FLOW-METER FOR EXTRACORPOREAL CIRCULATION

SIR,—We were interested to read of the extracorporeal-circulation blood flow-meter described by Dr. Nixon (Nov. 14). Several of our associates have made similar suggestions, but we do not agree that such a device gives a reliable guide to the blood flow-rate under clinical conditions, although it makes a useful alarm for high line pressures.

During 65 experimental and clinical cardiopulmonary bypass procedures, we have noticed fluctuations of up to 100 mm. Hg in the line pressures while the flow-rate remained constant. An occlusive setting has been used on a De Bakey pump on $^3/_8$ in. or $^1/_2$ in. internal-diameter 'Tygon' tubing to pump flows of 80–120 ml. per kg. per min. through cannulæ 3–5·8 mm. × 4 cm. for procedures lasting up to two hours. Mean arterial blood-pressure was monitored in an internal mammary or branchial artery by a pressure transducer and ranged from 85 to 100 mm. Hg, while line pressures ranged from 180 to 380 mm. Hg.

In the laboratory the pressure drop is indeed due to the constriction of the cannula, but in the body an important factor is vascular tone, especially as it affects the artery directly adjacent to the cannula. Should the flow rise over approximately 3 litres per min. in $^3/_8$ in. internal-diameter tubing, the change to turbulent flow will cause a disproportionately large increase in the pressure measured at the filter-chamber.

Department of Anesthesiology,
Hartford Hospital,
Hartford, Connecticut.

I. A. SLOAN.

INFLUENZA AND HEART-DISEASE

SIR,—I should like to refer to Dr. Bourne and Dr. Wedgwood's paper[1] on heart-diseases associated with influenza, and to Dr. Apley's letter.[2]

We have observed a respiratory infection in a native male child of $2^1/_2$ years which we considered as influenza because it occurred at the tail-end of an epidemic, and also because the histopathological findings in the lungs and heart suggested a viral infection. The child developed congestive heart-failure in the second week of his illness and died from it.

This might be of interest to people who have investigated the association of heart-disease with influenza, so we submit briefly the pathological report by Dr. T. H. Vickers, of the University of Queensland.

Lung.—There is slight hæmorrhagic consolidation of lung parenchyma with probable œdema and a peribronchial mononuclear-cell infiltration. Patchy intra-alveolar phagocytes are seen in some fields and the alveolar walls are rather thicker than normal suggesting the existence of mild passive congestion. As well there is evidence of a lobular pneumonia of indeterminate type.

Heart.—There is probable hypertrophy of most muscle-fibres in

1. Bourne, G., Wedgwood, J. *Lancet*, 1959, i, 1226.
2. Apley, J. *ibid.* p. 1282.

the heart and undoubted hypertrophy of some, so that the cardiac enlargement can be regarded as due to an increase in the bulk of the myocardial fibres and probably not due to œdema. This hypertrophy is accompanied by a slight but patchy mononuclear-cell infiltration most marked in the connective tissue around some of the blood-vessels and in the subserosa. The cellular infiltration is much more suggestive of a very mild myocarditis than an ischæmic lesion.

Department of Public Health,
Mount Hagen,
Western Highlands District,
Territory of Papua and New Guinea. L. E. PETRAUSKAS.

NATURAL HISTORY OF CAVERNOUS HÆMANGIOMATA

SIR,—It was sad to see Dr. Simpson's valuable and careful analysis of hæmangiomata (Dec. 12) receive such hostile criticism in recent letters. Dr. Colin-Jones (Jan. 2) writes airily of "misleading statistics", but cannot show that Dr. Simpson's observations (or deductions) were in error. He says "large numbers must be studied", but quotes with approval a series of 135 untreated cavernous lesions, while the paper he criticises deals with a slightly larger number. He himself reports 814 cases which received X-ray therapy; he mentions that 200 required treatment "after the 5-year period" but he is curiously vague about the precise results. He further confuses his own position by saying in one place "all are agreed that cavernous angiomas disappear in the course of time"; but a little later he thinks "there is a great tendency to exaggerate the frequency".

Dr. Simpson has in fact much well-informed dermatological opinion on his side; he also has the support of most plastic surgeons who, reluctant to carry out operative treatment which may give inferior results to those achieved by natural regression, still insist that the child is kept under close observation; they are thus in a position to intervene on rare specific indications. What plastic surgeons dread most in this context are the horrifying results which can follow the improper use of radiotherapy to "cure" non-malignant lesions in the young.

The Queen Victoria Hospital,
East Grinstead. C. R. MCLAUGHLIN.

SIR,—It is apparent from the letters of Dr. Colin-Jones and Mr. Denis Browne (Jan. 2) that Dr. Simpson has a hard task ahead if he wishes to convert all the treaters of cavernous hæmangiomata into non-treaters.

I am sure that his policy of no-treatment is a wise one although it requires far more courage and persuasion on the part of the clinician to convince anxious parents that nothing should be done.

In Sheffield, for the past ten years, all the dermatologists have adopted a no-treatment policy for cavernous hæmangiomata. It has, therefore, been impossible for patients to leave one clinic and go to another where they would be treated. The radiotherapists, who include Dr. Walter, the author of a controlled trial [1] of radiation and no-treatment in 1953, have carried out the same policy. The only escape route for dissatisfied patients has been to the department of plastic surgery, and I understand that there has been no rise in the number of cases referred for operation during the ten years.

The dermatologists and radiotherapists have watched spontaneous clearing occur in the great majority of the cases and they amount to some 200 hæmangiomata per year. Resolution has been particularly striking in those cases which, by their size or site, give rise to the biggest problem and which present a formidable task for surgeon or radiotherapist. There are no extra hazards from awaiting spontaneous resolution and the cosmetic results are as good, if not better, than any form of treatment. There are dangers from radiation, for in the series of carcinomas of the thyroid reported by Wilson et al.[2], 4 had received radiation for nævi around the neck. There is also no evidence that radiation does more than slightly speed up natural resolution.

Dr. Colin-Jones' remark that hæmangiomata are common in adults is difficult to understand since that is certainly not the experience in this area. I believe that, as yet, no form of treatment is superior to spontaneous regression though it would be interesting to hear more of the results of Mr. Denis Browne's early surgery.

The Rupert Hallam Department
of Dermatology, Royal Infirmary,
Sheffield. I. B. SNEDDON.

SIR,—It would be helpful if Mr. Denis Browne would kindly clarify one or two points he has raised in his comments on the views of Dr. Simpson and others who have worked along the same lines before him.

With regard to the first statement that many dreadful disfigurements begin as tiny red spots either present at birth or appearing in the first month, could he produce evidence that the large disfiguring hæmangiomata do often grow from tiny strawberry marks? I have watched for the development for years and have never seen it happen, assuming therefore that the deeply situated hæmangiomata must arise subcutaneously. Be it noted that only one type of hæmangioma is discussed in Dr. Simpson's paper, "port wine" and systematised nævi being rigidly excluded.

Next he states categorically that in their earliest stages hæmangiomatous nævi are quite invariably dismissed as trivialities, but he does not say by whom. Does he mean parents, general practitioners, or dermatologists, or all three? The long and meticulous follow-up studies by dermatologists to which he refers in his opening remarks indicate at least that some dermatologists have accepted these nævi as a very serious responsibility.

Finally he says that while no early case has ever been referred to him by a general practitioner, "in spite of his preaching that a growing red spot on a baby's face is a surgical emergency", he has picked up a few and treated them. The results, he says, suggest that the process of regression can be started very early in the growing stage by producing inflammation in the abnormal tissues. Could he possibly enlarge on this experience and tell us what he does? Most of the dermatologists have discarded diathermy, cauterising, and the injection of chemical substances because they, to whom these cases are referred in numbers by practitioners, have found such methods unsatisfactory. It is precisely this fact that has prompted the natural-history studies during the past twenty years. Freezing for small strawberry nævi is evidently acceptable to some, but the outlook in these nævi when not treated has long been known to be so good that many think it wiser to let well alone. Few will use any kind of radiotherapy in infants except when it can hardly be avoided. Is there something else about which we have not heard?

London, W.1. G. B. DOWLING.

SIR,—The essential point at issue in this discussion is surely a simple one—is there any real risk involved in treating all cavernous nævi with X-rays or thorium X, because if there is no risk, it is surely the best policy to give all affected children the benefit of treatment until the day when it is possible to distinguish at an early stage between those lesions which are likely to resolve spontaneously and those which will persist.

1. Walter, J. *J. Fac. Radiol.* 1953, **5**, 134.

2. Wilson, G. M., Kilpatrick, R., Eckert, H., Curran, R. C., Jepson, R. P., Blomfield, G. W. *Brit. med. J.* 1958, ii, 929.

I have been irradiating nævi for nearly twenty years, having initially used what would now be regarded as a rather high dose of 600–800r at 100 kV, repeated after three months, but I have yet to see or hear of any permanent ill effect among my treated cases, numbering over 1000, including those treated in association with Dr. Colin-Jones. In a confined community such as this, one would expect to be made aware of any untoward sequelæ of treatment, and colleagues would not continue to refer cases were they not completely satisfied.

There is at present a swing away from the use of radiotherapy in non-malignant conditions, particularly in children, and while it is wise to keep in mind the hazards attending the irradiation of living tissues, few methods of treatment contain no possibilities of causing damage if improperly used, and it would be a great pity if patients of any age were to be deprived of beneficial treatment because of unjustified fears engendered by propaganda. The dosage given to a child with a nævus is less than would result from many X-ray examinations, measured as total-body dosage; and the local dose used now, of the order of 400r at 60–100 kV on small fields, has not shown any late changes in the skin, hair, or bone.

May I conclude that we should continue to use our clinical judgment in dealing with nævi and that we should not be swayed against active treatment by doubtful hopes of natural resolution.

Hove. E. MILLINGTON.

SIR,—The article by Dr. Simpson and the subsequent correspondence indicate the confusion which is caused by the terminology of hæmangiomata.

When Dr. Simpson talks about " cavernous hæmangioma " he is presumably referring only to the common " strawberry nævus ", a lesion which is typically confined to the skin, and we are in entire agreement with him that these lesions will always regress spontaneously and that no treatment is necessary. Since they always disappear spontaneously, it follows that any form of treatment will be credited with good results. It seems unlikely that injection of sclerosing substances, treatment by carbon-dioxide snow, and similar methods will result in harmful sequelæ, but in view of the late, serious, and quite unpredictable consequences of treatment by radiotherapy, it seems to us that the use of such a powerful agent is highly undesirable and can be justified only in the most exceptional circumstances.

We cannot agree with Dr. Colin-Jones that " strawberry nævus " is commonly seen in adults. None of the surgeons in this centre has ever seen such a lesion, although we have seen many other types of angiomata in adults. If Dr. Colin-Jones has failed to distinguish the different types of hæmangioma, the results of his treatment are impossible to evaluate.

We strongly advocate that the term " cavernous hæmangioma " should not be used for these common skin lesions, but that they be described by the homely but unmistakable term " strawberry nævus ".

Mount Vernon Centre for Plastic Surgery, Northwood, Middlesex. I. F. K. MUIR
T. L. BARCLAY.

ATRIAL FIBRILLATION IN CARCINOMA OF THE LUNG

SIR,—The association of arrythmia with carcinoma of the lung has prevously been noted, but the following case seems worth recording to stress the importance of what appears to be a little-known manifestation of the commonest form of cancer.[1 2]

A man of 55 complained for one year of dizziness on exertion, associated more recently with attacks of regular palpitations, beginning and ending suddenly. He admitted to cough and pain in the shoulder for the previous fortnight but had no other significant symptoms. He had atrial fibrillation, with an apex rate of 120 and a pulse deficit of 16.

The chest showed flattening and diminished movement in the left upper zone, with an impaired percussion note, diminished breath sounds, and a persistent localised rhonchus. There were no other significant physical findings.

A clinical diagnosis of bronchial carcinoma was made on the basis of the association of signs of left upper-lobe collapse with atrial fibrillation.

Radiography showed a large left hilar mass with upper lobe collapse and a trace of fluid at the left base. Tomograms demonstrated almost complete occlusion of the left upper-lobe bronchus. Electrocardiography showed uncontrolled atrial fibrillation. Repeated sputum examination for malignant cells was negative.

An attempt to restore sinus rhythm with quinidine succeeded only for a few hours, after which ventricular tachycardia supervened. It was therefore decided to slow the ventricular rate with digoxin.

His general condition deteriorated rapidly and he developed massive hepatomegaly and bloodstained ascites. A further E.C.G. before death showed that runs of atrial extrasystoles had developed, with varying PR interval.

He died seven weeks after first being seen. Necropsy confirmed the diagnosis. The growth arose in the left main bronchus and invaded the left atrium and compressed the left pulmonary vessels. The heart was otherwise normal. There were massive deposits in the liver.

There are two especially interesting features of this case:

(1) The fact that atrial fibrillation was the presenting feature.

(2) The fact that apart from the fortnight of cough and shoulder pain before attending outpatients, there were no respiratory symptoms throughout the course of the illness.

Since this patient was seen, I have seen a further case in which atrial fibrillation arose in a 75-year-old man with signs of left lower-lobe collapse. He deteriorated rapidly, and necropsy revealed a carcinoma of the lung which had invaded the pericardium and myocardium. There was no coronary atheroma.

My thanks are due to Dr. R. A. Hickling for his encouragement and for his permission to publish this account of his patient. I should also like to thank Dr. H. P. Clarke for making it possible for me to visit the patient at home.

London, N.10. W. L. ASHTON.

1. Fishberg, A. M. *Amer. J. med. Sci.* 1930, **180**, 629.
2. Levy, T. M. *ibid.* 1948, **36**, 312.

DIURNAL FLUCTUATIONS OF PLASMA FIBRINOLYTIC ACTIVITY

SIR,—Readers of the articles by Buckell and Elliot [1 2] may be interested in the following observations.

The diurnal fluctuations of fibrinolytic plasma activity were observed independently in our laboratories, and first described two years ago.[3–6] The fluctuations of fibrinolytic activity were tested on diluted oxalate plasma and euglobulins clotting with Ca^{++} addition and, furthermore, on thrombin clots of oxalate euglobulins, which do not form intrinsic thrombin. Samples of citrate-thrombin, free of plasma, were used. The daily fluctuations of fibrinolysis were most pronounced in the thrombin clots of oxalate euglobulins. The titre of antifibrinolysin did not fluctuate adequately in samples of plasma and sera taken during the day. The antifibrinolysin was tested on a system consisting of bovine plasma, fibrinogen, and citrate-thrombin. The titre was found to vary from 50 to 87 arbitrary units in samples of plasma taken in the morning and from 46 to 88 in samples taken at the height of the fibrinolytic

1. Buckell, M., Elliot, F. A. *Lancet*, 1959, i, 660.
2. Buckell, M., Elliot, F. A. *ibid.* p. 662.
3. Kaniak, J., Siwińska, M., Krakowska-Rechnicowa, J., Iwankiewicz, S., Kornaszewski, W. *Postępy Higieny i Medycyny Doświadczalnej*, 1957, **11**, 355.
4. Kaniak, J., Siwińska-Kotschy, M., Głogowska, I. *ibid.* 1958, **12**, 299.
5. Siwińska-Kotschy, M., Głogowska, I. *ibid.* p. 533.
6. Kowarzyk, H., Kotschy, M., Głogowska, I. *ibid.* 1959, **13**, 315.

activity. The respective figures in serum were 51 to 76 and 63 to 70 units. Thus, changes of the antifibrinolytic titre do not seem to be the cause of the diurnal fluctuations of fibrinolysis.

The highest activity of fibrinolysis was comparable to that observed in an emergency reaction after adrenaline and in a hypoxæmic state at low air pressure. The diurnal fluctuations are a stress reaction and they vary from person to person and in the same individual from day to day. The diurnal fluctuations do not appear in young males confined to bed—e.g., with fractures.

T.A.M. (tosyl-L-arginine methyl ester. HCl) esterase activity of plasma and serum does not fluctuate correspondingly.

Diurnal fluctuations may mask the effect of alimentary lipæmia on fibrinolysis.[7] When comparing small groups of persons examined with the euglobulin and diluted plasma-technique at fixed hours of the day, one fasting, the other one after a fat meal, no significant differences of fibrinolytic activity were found between the lipæmic and control groups, the diurnal fluctuations of lysis time being invariably superimposed on the presumed lipæmic effect. Our main interest was in the activating mechanism of fibrinolysis, and no further attempt was made to verify the effect of lipæmia on fibrinolysis.

The fibrinolytic activity of globulins from diluted and acidified human plasma is potentiated by the process of thrombin formation.[8 9] The time of fibrinolysis is shorter in spontaneously clotting euglobulins than in the thrombin clot of the euglobulins not forming intrinsic thrombin. The time of lysis, in our operative conditions, averaged 210 and 450 minutes respectively. In stress, the time of lysis of thrombin clots is decreased to about 160 minutes. In the state of increased fibrinolysis, however, the generation of thrombin does not induce a further rise of fibrinolytic activity. Thus, the fibrinolytic activity developed in stress obscures the fibrinolytic activity related to thrombin formation.

The data so far available support the view that a uniform activating mechanism acts in vivo in the fibrinolytic stress reaction and in vitro in thrombin-forming fibrinolytic systems.

HUGON KOWARZYK
JÓZEF KANIAK
MARIA KOTSCHY.

Ludwik Hirszfeld's Institute of Immunology and Experimental Therapy, Wrocław, Poland.

HOTELS OR HOSPITALS?

SIR,—I read with interest the article by Mr. Stallworthy (Jan. 9) on the subject of "hotel" accommodation following operation. Thanks to a generous benefactor, it was possible in June of last year to open a "continuation" unit attached to Kilmarnock Infirmary. It is hoped to publish at the end of a year's work of this annexe a full report of the economic and clinical advantages.

The building, now called Torrance House, is a former sanatorium, and has been converted into very comfortable "hotel" accommodation with adequate rest and recreation rooms and dining-rooms. Beds are available for 44 patients, at present allocated between general surgery (28) and general medicine (16). The 28 surgical beds are filled from 60 surgical beds in the parent hospital, which is within ten minutes' distance by ambulance. Patients are transferred to Torrance House as soon after operation as it is thought that they are fit to walk from the sitting-rooms to the dining-rooms. Thus hernia repairs, appendicectomies, and hæmorrhoidectomies are normally transferred on the second or third postoperative day, and gastrectomies, vagotomies, and cholecystectomies on the fifth day. There is no routine transfer; the fitness of the patient for the annexe is assessed on the day before the transfer. The patients are transported by ambulance from the parent hospital, and throughout their stay in the annexe they wear their own clothes.

No medical staff is resident in the annexe, but a direct telephone line to this parent hospital means that a house-surgeon is on immediate call. Nursing staff consists of one matron, two sisters, two full-time and two part-time staff nurses, two full-time auxiliary nurses, and four part-time assistant nurses.

During the short time that Torrance House has been in action the advantages set out by Mr. Stallworthy have become apparent. In the first six months 620 patients were transferred to the surgical beds from Kilmarnock Infirmary with the result that the general surgical waiting-list has come down in that time from 460 to 310 after years of being static or rising. The comfort, quietness, and access to gardens is appreciated by the patients, and early return to complete activity is hastened. It is surprising how well a fifth-day gastrectomy can play billiards!

No serious disadvantages have been encountered, but a certain self-discipline is required by those in charge of beds in the "hotel". As far as Torrance House is concerned, it has been written into the constitution that the maximum stay for patients is three weeks—this to prevent any temptation to use beds for chronic sick. We have made it a routine here for all surgical patients in the annexe to be seen daily by a consultant together with the registrar or a house-surgeon. This is necessary, not only for the purpose of clinical supervision, but in order to avoid giving the patients the impression that they are being "dumped" out of the main hospital.

The Infirmary, Kilmarnock. GAVIN J. RALSTON.

SIR,—How heartening to see in last week's *Lancet* a really imaginative article on the future planning of a hospital and home-care service. There are a good many nurses who also believe that the future of our health service will lie in acute central hospitals for the individual who needs and must have hospital care, plus convalescent aftercare units run on hotel lines, and a really well-organised, well-staffed domiciliary medical and nursing service.

One visualises "flying-squads" of nurses and doctors visiting people in their own homes, doing dressings, treatment, and so on. The "squads" would be based on the local authority. What a wonderful opportunity to train nurses and doctors! At present one of the most common criticisms levelled at our nurse-training by other countries is that British nurses "only nurse in hospital", a criticism that cannot be denied: but with the kind of service envisaged, trainee nurses and medical students alike would get immensely valuable training in caring for people in the ordinary social setting of their homes: a broadening and educational experience we could all do with early in our career. The acute centres would, of course, deal with all conditions requiring hospital care, for whatever cause. Again, the ideal training situation, where the student can have experience of all human ills under one roof—a really comprehensive training, with plenty of chance to specialise later.

For so long now I have thought about this idea as a sort of unattainable pipe-dream, regarded as fantastic if expressed, that it is really exciting to see it has already taken shape in other minds; though perhaps it is a little ironical that it has taken us about two hundred years to persuade people that hospital is the best place to be ill in, and now that this idea seems to have been well and truly sold to the suffering public there are signs of a move to re-educate them to prefer to be ill at home. Somehow I think the process is likely to take less time.

Tooting Bec Hospital, London, S.W.17. UNA V. BUDGE.

7. Greig, H. B. W. *Lancet*, 1956, ii, 16.
8. Kowarzyk, H. 6th Congress of the European Society of Hæmatology, Copenhagen, 1957, ii, 452.
9. Kowarzyk, H., Buluk, K. *Postępy Higieny i Medycyny Doświadczalnej*, 1959, 2, 1.

Obituary

WILLIAM ROBERT FEARON

M.A., M.B., Sc.D. Dubl., F.R.I.C.

Professor Fearon, who held the chair of biochemistry in the University of Dublin and was a member of the Irish Senate, died on Dec. 27 at the age of 67.

His father, the Rev. William Fearon, of Kells, died when he was a child and he was brought up by his mother. From St. Andrew's College, Dublin, he entered Trinity College in 1911 and started his medical studies soon afterwards. But he was such a versatile student (winning with equal ease medical scholarships, the Purser medal in physiology, and the vice-chancellor's prize in English verse, and taking an honours degree in the natural sciences) that he did not finally qualify till 1929. Meanwhile he had spent two years with an exhibition at Emmanuel College, Cambridge. In 1921 he was appointed to a fellowship at Trinity College, Dublin. There, though his chief duty was teaching physical chemistry, physiology, and biochemistry, he also gladly gave lectures in logic and examined in that subject. But the influence of Werner in Dublin and Gowland Hopkins in Cambridge had already determined him to make biochemistry his chief interest. He was appointed lecturer in 1921, and in 1934 a chair was created for him. In the same year the first edition of his well-known *Introduction to Biochemistry* appeared. Even with growing academic responsibilities his interests in the arts did not slacken, and his play *Parnell of Avondale* was successfully produced at the Abbey Theatre in 1937.

Some of Fearon's earliest biochemical work was related to urea, which was Werner's special interest, and to vitamins. But it was not long before another side of his nature began to express itself in his work. He was early elected honorary professor of chemistry to the Royal Hibernian Academy, and his love of colour, as of the artistic, combined to make him an ideal choice. In his scientific work the charm which colour held for him began to express itself in the development of a series of colour reactions for the identification of a wide range of compounds of biological interest.

In 1943 he was first chosen by the university electorate as their representative in the Irish Senate.

R. A. Q. O'M. writes:

"Of his election to the Senate, Fearon was very proud and, curiously, this honour provided him with more pleasure and satisfaction than many others which he had won during his distinguished career. The university electorate continued to the end to return him and, in the special circumstances which govern this election, his repeated return signified that his former students supported him with their first preference votes almost to a man. Of course, he drew support from other sources as well, but no doubt the memory of his inspired teaching must have remained to prompt them as they marked their voting-papers. His lectures were memorable not alone for their scientific content but for the beauty of the language and the clarity of expression, enlivened by artistic, musical, theatrical, and poetic reference, with which they were delivered, and when he spoke in the Senate his audience was likewise held. Standing at Fearon's graveside an elder of the House, well tried in politics, said, 'He could make a speech. He had a nice wit and a sense of irony, too.'

"His wit and irony, never malicious though often happily pointed, were a charming asset to Fearon at the table or on the platform. He was much sought after on such occasions as opening meetings of societies or when the time had come to lionise the distinguished visitor. He appreciated good food and wine, but as time went by he became more difficult to entice to the festive occasion. Great was the reward of success in such enticement, however, for an evening in his company never flagged. Even the chance and seemingly aimless remark of the least important of the guests was likely to be taken at more than its value and built by him into a subject for serious consideration in a happily light vein. For it was one of his characteristics that he was always ready to listen to others, to see good in their often faltering thoughts and gently to amplify them so that they rapidly grew, like a tree, to have many branches.

"Fearon remained a bachelor. He lived with his mother, to whom he was greatly attached, and who died only a few years ago. His home life was simple, though he had one inclination to extravagance—in his cars. In the 'twenties he could be seen as the sole occupant of a long Lancia, later of a Bentley, and in the final years, as befitted his Senatorial rank, of a Rolls. Towards the end it was apparent that he was becoming dissatisfied with the crudities of modern life and in particular felt unhappy about the decline in manners in our times. His was a generous, courteous, and upright nature, and he was incapable of the rudely aggressive or of the plausibly dishonest. For him 'the larger heart, the kindlier hand'."

Dr. J. E. A. UNDERWOOD

R. E. S. writes:

"The Medical Officers of Schools Association owes Dr. Underwood a particular debt. He realised that, though doctors at public schools had for a long time usually occupied the important offices, the association had the welfare of all types of boys and girls at heart. He was the first senior official of the Ministry of Education to take an active part in our discussions and the first to become president (in the 68th year of our foundation). From 1952 to 1953 he presided with great dignity and we came to know that behind his humility lay great knowledge especially of the handicapped child. His name will be remembered in many ways but it will live chiefly for the Underwood report on the maladjusted child."

Public Health

Safety Code for Use of Ionising Radiations

REVISIONS to the draft code, issued in July, 1957, for the protection of workers engaged in operations involving the production, emission, or use of sealed sources of ionising radiations are contained in the second preliminary draft of special regulations [1] published this week.

The original draft included a general invitation to industry, associations, and others concerned to make comments on the proposed regulations, and many suggestions were received and amendments arising from the observations have been included in the new draft.

The schedule specifying the maximum permissible radiation doses has been remodelled taking account of the views of the Medical Research Council and the revised recommendations of the International Commission on Radiological Protection. It has been simplified by restricting it to certain ionising radiations which are ordinarily met with in industrial work with sealed sources. There are new provisions dealing with tests for personal exposure and medical supervision, with the examination of persons employed in the processes, and the procedure to be adopted where workers employed in the processes move from one factory to another. Fuel elements used or intended to be used in a nuclear reactor will not be covered by these regulations, which also exclude from their application ionising radiations used for medical purposes in factories or rooms specially set apart. Comments on the new draft are requested by April 15.

Arsenites in Agriculture

Mr. John Hare, Minister of Agriculture, Fisheries, and Food, has announced that the use of alkali arsenites in agriculture is to be restricted. Speaking at Wells on Jan. 6, he said:

"The potential risks here are particularly wide because of the large number of people involved and the danger to cattle. The Advisory Committee on Poisonous Substances, which deals with agriculture and food storage, recommended that their use should be voluntarily banned . . . agreement has now been reached that the manufacture of alkali arsenites for use in this country as haulm destroyers and weed killers shall now stop, and that after this year's potato harvest the agricultural and ancillary industries will withdraw these arsenites from agricultural use. This voluntary ban will not apply to sheep or cattle dips, or to the use of lead arsenate on fruit trees."

1. Factories (Ionising Radiations). Special Regulations. Second Preliminary Draft. H.M. Stationery Office. Pp. 20. 1s. 3d.

Notes and News

RESEARCH ON INTERFERON

A SUBSTANCE "with many of the properties of a wide-spectrum viral antibiotic", interferon was discovered at the National Institute for Medical Research during study of the virus interference phenomenon.[1] In his investigations with colleagues, Dr. Alick Isaacs has shown that it is a protein, of low toxicity to tissues, which is apparently non-antigenic and able to inhibit the growth of a large variety of viruses. Two papers on its action appeared in our columns last September.[2]

Before the possible therapeutic use of interferon could be studied, much basic research on its properties had to be done; but a stage has now been reached when the development work that must precede therapeutic trial can be undertaken. So as to get an answer quickly, the Medical Research Council have entered into an arrangement for collaborative research with three firms in the pharmaceutical industry—namely, Glaxo Laboratories Ltd., Imperial Chemical Industries Ltd., and the Wellcome Foundation Ltd.—the National Research Development Corporation also being a party to the agreement. The work covered by the agreement includes research into the pilot-scale production of interferon required for research purposes and studies of its effect in experimental virus infections of animals. Whether it is used in therapeutic trials in human beings will depend on the results of these experiments.

A NEW INSTRUMENT

THE official existence of the new organisation and methods unit of the Ministry of Health is a sign that work study has been accepted as an effective aid to the administration of the National Health Service. Skill in using new tools usually increases with practice, and in work study the relatively close-knit hospital services will probably be easier terrain than, say, the diffuse and often highly individual arrangements hopefully covered by the orderly title of "general medical services". The National Association of Hospital Management Committee Group Secretaries have, therefore, been considering work study in the hospital service.[3] They are firmly in favour of its adoption because they believe that properly applied it may save some money (though not perhaps so much as expected, for it will sometimes lead to redeployment rather than reduction of resources) and that it will also encourage the staff to take a more informed interest in their work and often improve their working conditions. It will provide badly needed facts on priorities and needs for capital development.

The report suggests that one of the common objections to work study—that it impairs staff morale—is caused by faulty application. With tact and the right approach this difficulty should usually be avoided. Nor should work study properly conducted bring a risk of reducing services to patients, for a rational assessment of the activities of a hospital should recognise such small acts as cups of tea and reassuring talks with patients and relatives as part of a good nurse's true duties. On their frank appraisal of these difficulties is based the Association's recommendation that the most suitable subjects for work studies, at least at first, are the indirect services to the patients, such as laundry and catering, and the nonclinical organisation of other parts of the hospital, such as appointment systems or records. Judging by the reports already issued this policy has been accepted by the Ministry's unit.

Difficulties would also be avoided, the Association suggest, if the study was conducted from within the hospital rather than from without, by someone who understands the background and is familiar with medical and nursing problems. In their view it should be done at H.M.C. level, and all senior hospital staff members should attend short courses on work study, and selected officers, of at least senior administrative grade, who would actually conduct the studies should attend a three-month course. It will be interesting to see how other hospital authorities, such as regional hospital boards and the Ministry, react to this last suggestion. Certainly much of the rest of this thoughtful report will win their approbation.

1. Isaacs, A., Lindenmann, J. *Proc. roy. Soc.* B, 1957, **147**, 258.
2. Isaacs, A., Westwood, M. A. *Lancet*, 1959, ii, 324; Porterfield, J. S. *ibid.* p. 326.
3. Copies of the report are available from the hon. secretary, Mr. S. G. Hill, LL.B., F.H.A., General Hospital, Northampton.

AMATEUR BOXING

A HANDBOOK lately issued by the London Amateur Boxing Association[1] is short but not everywhere clear or to the point. What is clear, however, is that the Association considers that the risks of boxing are not serious. The statement that "boxing represents the only opportunity in man of observing repeated head injuries in an almost experimental setting" presumably implies that the "experiment" should continue until the effect of these injuries on the brain can be fully and accurately assessed. But is this "experiment" either justifiable or necessary? Is there not overwhelming evidence that even trivial head injuries can cause serious brain damage? The boxer is exposed to injuries which are deliberate, repeated, and often severe enough to cause loss of consciousness. If the nature and extent of the damage they cause has not yet been accurately assessed, should we not, nevertheless, give the brain the benefit of any doubt? Enlightenment of the public on the dangers of boxing can come only from the medical profession; and an authoritative statement by a detached body of medical experts would do much good.

NUTRITION IN AFRICA

IN Angola in 1956, the Commission for Technical Cooperation in Africa South of the Sahara held a conference on nutrition. The second volume of the report of this conference,[2] written in French, English, and Portuguese, deals with improvements of national diets with protein-rich foods, agriculture and nutrition, public-health services and education in nutrition, treatment of ariboflavinosis in schoolchildren, the digestibility of cassava, and many other subjects. Though the many authors and different styles of presentation make it difficult to read, it contains much valuable information; and a small but useful index makes it a good reference for nutritional problems in Africa.

1. Medical Aspects of Amateur Boxing. Issued by the London Amateur Boxing Association, 69, Victoria Street, S.W.1. 1959. Pp. 64. 2*s.* 6*d.*
2. Vol. 2, pp. 877. Obtainable from Abbey House, 2, Victoria Street, London, S.W.1.

University of London

Dr. G. V. R. Born, research officer at the Nuffield Institute for Medical Research and departmental demonstrator in pharmacology in the University of Oxford, has been appointed to the Vandervell chair of pharmacology tenable at the Institute of Basic Medical Sciences.

Dr. Born qualified M.B. at the University of Edinburgh in 1943. Subsequently he entered the R.A.M.C., in which he worked as a pathologist. He was demobilised in 1947, and the following year he went as a Medical Research Council student in research methods to Oxford, where he studied the bacteriolytic enzymes of streptomyces. From 1951 he was for two years a member of the Council's scientific staff, working in the toxicology research unit at Carshalton. He returned to Oxford in 1953. He graduated D.PHIL at Oxford in 1951, and M.A. in 1956. Dr. Born's published work includes papers on smooth muscle and on blood platelets, and a chapter on the effects of injury on metabolism in Florey's *General Pathology*.

Dr. D. L. J. Bilbey, assistant professor of anatomy in the University of Toronto, has been appointed to a readership in anatomy tenable at King's College.

Dr. R. M. H. McMinn, lecturer in the University of Sheffield, has been appointed to a readership in anatomy tenable at King's College.

University of Liverpool

A symposium on general practice and psychiatry will be held on Saturday, March 26, at 10 A.M., in the University New Medical School, Ashton Street, Liverpool. Tickets may be had from the director, Department of Studies in Psychological Medicine, 77, Bedford Street South, Liverpool, 7.

University of Birmingham

Dr. R. F. Fletcher has been appointed lecturer in medicine.

University of St. Andrews

Dr. John Simpson has been appointed senior lecturer in public health and social medicine in Queen's College, Dundee.

Royal College of Physicians of London

On Tuesday and Thursday, Feb. 2 and 4, Dr. L. G. Norman will give the Milroy lectures. He will speak on the medical aspects of the prevention of road accidents. On Tuesday and Thursday, Feb. 23 and 25, Prof. D. E. Denny-Brown will give the Croonian lectures. He will speak on diseases of the basal ganglia and their relation to disorders of movement. All the lectures will be given at 5 P.M. at the college, Pall Mall East, S.W.1.

Royal Faculty of Physicians and Surgeons

At a meeting on Jan. 4, with Mr. Arthur Jacobs, the president, in the chair, the following were admitted to the fellowship of the faculty:

Majid Ali Jafri *qua physician;* Mohamed Magid Ismail Fakhr, C. N. Hudson, D. G. Jones *qua surgeon.*

College of General Practitioners

Public Welfare Foundation Prize.—Six prizes (£40 each) are offered to encourage senior medical students to study the diagnosis and management of patients in the setting of general practice. Particulars may be had from the secretary of the college, 41, Cadogan Gardens, London, S.W.3. The closing date is May 1.

International Hospital Federation

Dr. J. C. J. Burkens, medical director of the Oude en Nieuwe Gasthuis, Delft, Holland, has succeeded Captain J. E. Stone as hon. secretary and treasurer of the Federation. The secretariat remains in England at 34, King Street, London, E.C.2.

Medical Costs in South Africa

Dr. Albert Hertzog, the South African Minister of Health, has announced the appointment of a commission to inquire into the factors responsible for the high cost of medical services and of medicines and into ways in which these costs can be lowered. The Minister said:

"Families in the middle-income group are especially hard hit. On the one hand they cannot, as in the case of the less privileged, receive free medical treatment; and on the other hand they are not financially in a position to spend large sums of money on treatment. It often happens that, because of the serious illness of one member, a whole family is crippled financially for years. Others again neglect their health with tragic results because they cannot manage the high expenditure."

Professor J. A. B. Gray will give his inaugural lecture on Tuesday, Feb. 23, at 5.30 P.M. at University College, Gower Street, London, W.C.1. He will speak on the place of physiology in university education.

The Polar Medal has been awarded to Dr. R. L. Willing for service as medical officer to the Australian National Antarctic Research Expedition to Mawson, 1957.

Dr. P. K. Basu has been appointed the Stapells director of ophthalmic research in the University of Toronto.

The Biochemical Society will hold a meeting on Saturday, Jan. 23, at 10 A.M. at the London Hospital Medical College, Turner Street, E.1.

The closing date for entries for the Jean Hunter Bequest of the Royal College of Physicians of Edinburgh (Advertisers' Announcements, Jan. 9, p. 37) has been advanced to June 30, 1960.

The General Medical Council has published the third edition of their *List of Approved Hospitals and Institutions and Recognised House Officer Posts.* Copies (7*s.* 6*d.*) may be had from the registrar of the Council, 44, Hallam Street, London, W.1.

CORRIGENDUM: *Resistance to Ketosis in Obese Subjects.*—In the paper by Professor Kekwick and his colleagues (Dec. 26) a sentence near the bottom of column 2 on p. 1158 should read: "Blood leaving the brain has a respiratory quotient of 0·97 and the rate of utilisation of glucose is about 5·5 mg. per minute per 100 g. brain".

Diary of the Week

JAN. 17 TO 23

Monday, 18th

UNIVERSITY OF LONDON
5.15 P.M. (Westminster Medical School, Horseferry Road, S.W.1.) Prof V. M. Trikojus (Melbourne): Aspects of Thyroid Biochemistry.
POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Mr. N. W. Please: Elements of Statistical Methods.
HUNTERIAN SOCIETY
8.30 P.M. (Mansion House, E.C.4.) Prof. C. Walton Lillehei (Minnesota): Recent Progress in Open Heart Surgery. (Hunterian lecture.)
UNIVERSITY OF ST. ANDREWS
4 P.M. (Queen's College, Dundee.) Prof. G. H. Bell: Healing of Fractures.

Tuesday, 19th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Dr. John Badenoch: Steatorrhœa in the Adult. (First of two Goulstonian lectures.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. H. B. Stoner: Biochemical Response to Injury.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Dr. Elizabeth Tylden: Obstetrical Prognosis and Mental Illness.
WEST END HOSPITAL FOR NEUROLOGY AND SURGERY, 91, Dean Street, W.1
5.30 P.M. Mr. Joseph Minton: Ocular Manifestations in Clinical Neurology.
SOUTH WEST LONDON MEDICAL SOCIETY
8.30 P.M. (Bolingbroke Hospital, S.W.11.) Mr. E. H. Miles Foxen: Recent Advances in the Relief of Deafness.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Mr. J. B. Pennybacker: Observations on Trigeminal Neuralgia.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Prof. Adam Patrick: Encephalitis Lethargica.

Wednesday, 20th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8.15 P.M. *General Practice.* Dr. Lawrence Dulake, Mr. Bryan Brooke, Miss Muriel Powell: Early Ambulation.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. Hermann Lehmann: What is Thalassæmia?
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Henry Haber: Clefts, Vesicles, and Bullæ.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. N. Lloyd Rusby: Sarcoidosis.
UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Queen's College, Dundee.) Mr. I. S. Smillie: Physiology of the Knee-joint in Relation to Disease and Injury.

Thursday, 21st

ROYAL COLLEGE OF PHYSICIANS OF LONDON
5 P.M. Dr. John Badenoch: Steatorrhœa in the Adult. (Second of two Goulstonian lectures.)
BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. Sir George Pickering: Fever and Pyrogens.
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26 Portland Place, W.1
7.30 P.M. Dr. C. E. Gordon Smith, Mr. P. F. Mattingly, Prof. C. D. Darlington: Arthropod-borne Diseases.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.15 P.M. (11, Chandos Street, W.1.) Prof. Martin Roth: Problems of Mental Health in the Aged.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Queen's College, Dundee.) Dr. R. E. Steiner: Radiology and the Portal Circulation.

Friday, 22nd

ROYAL SOCIETY OF MEDICINE
5 P.M. *Pædiatrics.* Prof. R. A. McCance: Development of Acid-base Control in the Newly Born. Mr. J. H. Doggart: Eye Changes in Systemic Pædiatric Disease. Dr. Giuseppe Pampiglione: Neurophysiological Aspects of Cerebral Ischæmia.
POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. S. O. Aylett: Diffuse Ulcerative Colitis with Especial Reference to Treatment by Ileo-rectal Anastomosis.
4 P.M. Mr. N. W. Please: Elements of Statistical Methods.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Mr. Norman Asherson: Upper Œsophageal Disease.
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
4.30 P.M. Dr. W. H. McMenemey: Pathology of Presenile Dementia.

Appointments

BARTON, R. W. A. C., M.B. Lond., M.R.C.P., D.P.M.: physician-superintendent, Severalls Hospital, Colchester, Essex.
GREVILLE, ELINOR M., M.R.C.S., D.P.H.: district M.O.H., Montgomeryshire (Llanfyllin, Montgomery, Welshpool, and Forden districts).
YOUNG, J. G. M.B. Glasg., D.P.H.: assistant M.O., Dumfriesshire.

Birmingham Regional Hospital Board:

ALDERSON, D. A., M.B., B.SC. Lond., D.M.R.D.: part-time consultant radiologist, Stafford group of hospitals.
BROOKS, WILLIAM, M.B. Lond., F.F.A. R.C.S.: part-time consultant anæsthetist, Hereford group of hospitals.
DYSON, M. L., M.R.C.S., D.M.R.T., D.M.R.D.: part-time consultant radiologist, Wolverhampton and Dudley and Stourbridge groups of hospitals.
PARKER, R. G. F., M.D. Cantab., D.P.H.: consultant pathologist, Birmingham (Selly Oak) and Birmingham (sanatoria) groups of hospitals.